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PROSTAGLANDINS

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The Use of PGs in Human Reproduction

Summary. Recent studies from around the world show that prostaglandins play a major role in human reproduction and indeed in many other vital processes. Clinical application of PGs now includes management of obstetrical complications and cervical priming as well as induction of labor and termination of first and second trimester pregnancies. Further research is focusing on new prostaglandin analogues derived from naturally occurring PGE_1, PGE_2, and $PGF_{2\alpha}$. These analogues are longer lasting and more potent. Because they are more specific in their impact, they are less likely to produce undesirable side effects. Drugs that inhibit PG synthesis or block the action of PGs are being investigated to treat dysmenorrhea and have a wide range of potential clinical uses.

Current clinical uses of prostaglandins in reproductive health care depend on at least two different actions of PGs:

(1) as a smooth muscle stimulant, directly or indirectly producing or augmenting uterine contractions;
(2) as a priming agent, altering and softening the structure of the cervix to bring about dilation.

A third possible role is as a luteolytic agent — that is, an agent inhibiting the corpus luteum from producing the progesterone necessary to maintain pregnancy. This action, although documented in various animals, has not been proven in humans but remains a research goal.

Although widely hailed in the late 1960s as a potential abortifacient, PGs were first approved by drug regulatory agencies for induction of labor as well. PGE_2, given intravenously, extraamniotically, orally, or vaginally, has proved an acceptable substitute in many cases for the customary procedure of rupturing the membranes (amniotomy) and intravenously infusing oxytocin. The 0.5 mg oral tablets approved for marketing in 1975 in Britain are popular with both women and health personnel because they avoid the more confining intravenous procedure. Medical practice differs with respect to induction of labor. In the US induction is discouraged except for clear medical reasons, and intravenous infusion of oxytocin is preferred to provide immediate control over dosage. Such control is especially important with prostaglandins since the margin between an effective dose and an overdose (which might cause fetal distress) is narrow.

The tablets, as well as suppositories and PG gels, have also been used vaginally and intracervically to soften, or prime, the cervix before induction of labor. Since a soft, effaced, and dilated cervix is a key factor facilitating delivery, the use of PGs to speed this process is an important clinical application.

To date, PGs have been least successful in the role originally expected to be their most important application — terminating early first trimester pregnancies without need for surgical procedures. Chiefly because of the incidence of incomplete abortions and also because of the relatively long time required and the frequent side effects of pain, vomiting, and diarrhea, many clinicians have been reluctant to substitute PG injections or suppositories for vacuum aspiration, which is now the standard medical procedure for termination of first trimester pregnancy.

Testing New Analogues

Studies are underway using several new PG analogues which are potent over a longer time period and produce fewer gastrointestinal side effects. To terminate very early pregnancies (up to seven weeks from the last menstrual period) some of the new analogues, in suppository and injection form, are now approaching vacuum aspiration in effectiveness. For example, sulprostone has proved 96 percent effective in inducing menstrual bleeding an average of three to four hours after intramuscular injections. So far PGs have been available only through hospital pharmacies or on an investigational basis. Therefore, it is impossible to determine whether, given a choice, women would prefer a rapid surgical procedure such as vacuum aspiration performed in a clinic or a longer process of menstrual induction by intramuscular injection or self-administered suppositories. Additional research is needed, not only on the safety and effectiveness of different PG analogues,

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but also on the needs and preferences of the women using these services in different countries. In the long run, acceptability, costs, and, above all, availability will play an important role in determining which procedures are used.

These analogues are also being evaluated for terminating second trimester pregnancy, a more difficult procedure. Another new $PGF_{2\alpha}$ analogue, 15-methyl-$PGF_{2\alpha}$ (tromethamine salt), was licensed in 1979 in India for use by the intramuscular, intraamniotic, and vaginal routes and in the US as an intramuscular injection. It is more effective than natural PGs, but gastrointestinal side effects still occur in the majority of women. The analogue in methyl ester form has been investigated in suppositories, with effectiveness rates of 90 percent and above but no improvement in rates of incomplete abortion and side effects.

Combination procedures are now frequently used for second trimester terminations. For example, lower doses of intraamniotic $PGF_{2\alpha}$ are being administered together with oxytocic agents such as urea. Laminaria to help dilate the cervix are now utilized with PGs as well as with vacuum techniques. These combinations reduce the time interval to fetal expulsion and minimize the risk of injury to the cervix.

Already $PGF_{2\alpha}$ frequently is injected intraamniotically for second trimester terminations instead of the customary procedure of hypertonic saline instillation. In the US about 15 to 20 percent of second trimester abortions are now performed with PGs, including an increasing number of procedures where PGs are combined with other uterus-stimulating agents. But controversy over the relative safety of various procedures has not been resolved. In data gathered by the World Health Organization, the US Center for Disease Control, and the Indian Council of Medical Research, certain complications — infection, bleeding, and rehospitalization — are more frequent with $PGF_{2\alpha}$ than with saline. US data suggest that mortality with the two methods is not significantly different. Indian data show higher mortality with saline. A third procedure — dilatation and evacuation (D&E) — is also under study and is being used safely and effectively in the US by qualified and experienced practitioners up to 16 weeks of gestation. Debate continues over which technique is preferable at what period of pregnancy and under what conditions, but it is too early to reach conclusions. One incontrovertible finding is that the risks of abortion increase in direct proportion to the length of gestation. In the US, for example, mortality ranges from 0.5 per 100,000 procedures before 8 weeks to 9.9 between the 13th and 15th weeks, 16.3 between the 16th and 20th weeks, and 27.9 after 21 weeks.

PGs and Obstetrical Complications

Prostaglandins have become a promising method for induction of labor in cases of intrauterine death and similar obstetric complications. They are more effective than oxytocin and less dangerous than saline and may eliminate need for surgical intervention. In a large study with PGE_2 suppositories, over 95 percent of women with fetal death were delivered successfully and in a short time. Intramuscular injections have proved effective in small studies, but experience is too limited to indicate the best route of administration. D&E is also used now for missed abortion. PGs have been used successfully to initiate labor in cases of anencephaly (a congenital defect in which much of the fetal brain is absent) and, followed by curettage, in cases of hydatidiform mole (a benign cystic tumor derived from conceptual tissue).

An important new use of PGs is to stop postpartum bleeding. Clinicians have found that 15-methyl-$PGF_{2\alpha}$, injected intramuscularly, is highly effective in managing this common complication of delivery.

The same qualities that make PGs useful in bringing on labor and abortion probably produce the menstrual pain and discomfort known as dysmenorrhea. Antiinflammatory drugs which inhibit the synthesis of prostaglandin have been used successfully to treat both primary dysmenorrhea and some types of secondary dysmenorrhea, for example, after IUD insertion. For the many women who have suffered this kind of debilitating menstrual pain and associated malaise, research on PGs has helped produce safe, specific, and welcome relief. PG synthesis inhibitors are also used to stop premature labor.

It is increasingly clear that both PGs and PG inhibitors play an important role in the reproductive process. As the study of PGs continues and as new analogues are developed and tested, the clinical uses of these remarkable and ubiquitous compounds will undoubtedly multiply. Research on prostaglandins demonstrates once again that scientific advances often come not only from the expected directions but also from unanticipated new applications. **End of Summary.**

Because of the specialized scientific nature of this report, the full text will not be translated into other languages. A summary version will be available in French, Spanish, Portuguese, and Arabic. Additional copies of the English text will be provided on request.

BACKGROUND

The first reference to a substance in the female reproductive system that might have been prostaglandin was an account in 1920 from Vienna of a menstrual poison — a substance in perspiration on the hands of a menstruating woman that had the power to wither roses (385). In several experiments the Viennese physician B. Schick also tried to test the old wives' tale that a menstruating woman could prevent bread from rising or wine from fermenting, but the results were inconclusive (385). Soon thereafter, other researchers observed that something in breast milk and in acetone extracts of menstrual fluid was toxic to primroses (307, 308). Vernon R. Pickles subsequently repeated the experiment with primroses and identified prostaglandins in menstrual fluid as the "menstrual toxin" involved (354, 355).

The official history of prostaglandins usually begins in 1930, when Raphael Kurzrok and Charles C. Lieb in the US reported that semen caused strips of human uterus to relax or contract (256). In the mid-1930s Maurice Goldblatt in the United Kingdom (164) and Ulf S. von Euler in Sweden (470) independently noted that secretions and extracts from prostate glands and seminal fluids lowered blood pressure in animals and stimulated the uterus. In 1935, von Euler coined the name "prostaglandin" to denote the active principle which he at first thought was secreted by the prostate gland (471). Subsequently it was established that prostaglandins are not a single compound produced by the prostate gland, but rather a group of 14 related polyunsaturated fatty acids — 20-carbon molecules each consisting of a 5-carbon ring and two side chains — produced by the male seminal vesicles and most other mammalian tissues.

By 1960 Sune Bergström and colleagues at the Karolinska Institute in Stockholm had isolated two different prostaglandin compounds: the one more soluble in ether was named PGE; the one more soluble in phosphate buffer (spelled with an F in Swedish), PGF (24, 25). With financial assistance from the Upjohn Company, Bergström procured some 4,200 kg of sheep seminal vesicles for analysis. From this biological material he was able to determine the chemical structure of several PGs (23).

PGs have been classified into so-called primary PGs — including PGE_1, PGE_2, PGE_3, $PGF_{1\alpha}$, $PGF_{2\alpha}$, and $PGF_{3\alpha}$; other natural PGs, such as PGAs and PGBs; several equally potent endoperoxide precursors, such as PGG_2 and PGH_2; and the much less active PG degradation products (metabolites). Related to the PGs are two recently discovered classes of powerful regulators of blood clotting, the prostacyclins (PGI_2), having an extra 5-membered endoperoxide ring between Carbon 6 and Carbon 9, and the thromboxanes, with two endoperoxide rings between Carbons 9 and 11, and 11 and 12 (see Figure 1 and Figure 2, p. G-80).

Synthesis and Research Progress

Until the mid-1960s, research on PGs was limited by the difficulty and expense of isolating a sufficient quantity of the substance from animal material. In 1965 both the Karolinska research group (21), working with Unilever Research Laboratories in the Netherlands (467), and the Upjohn Company (13) developed a biosynthetic laboratory technique to produce PGs through an enzymatic conversion of fatty acids. By the late 1960s both Upjohn (357) and Harvard University chemist E.J.

Raphael Kurzrok and Charles C. Lieb are shown recording uterine contractions on a large kymograph in the New York laboratory where they first investigated the action of prostaglandins, circa 1930.

Corey (101, 506, 518) had devised a commercially feasible total synthesis of PGs, which greatly facilitated mass production for laboratory and clinical research. In tandem with improved production came improved means to measure PGs. First, the cumbersome bioassays of animal organs gave way to the highly technical process of gas-liquid chromatography with mass spectrometry, capable of measuring nanogram quantities (169, 171, 377); then this in turn gave way to the more efficient radioimmunoassays, which can measure picogram quantities (102, 170, 244, 283, 284).

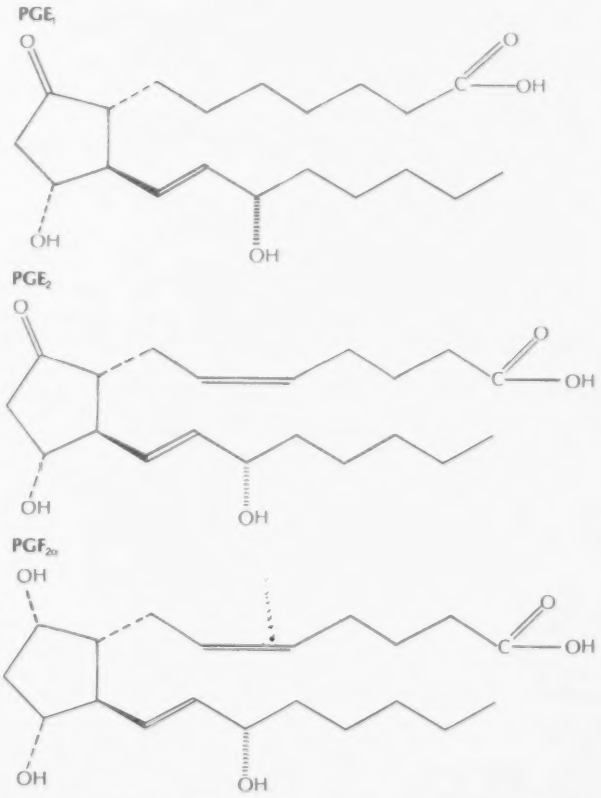
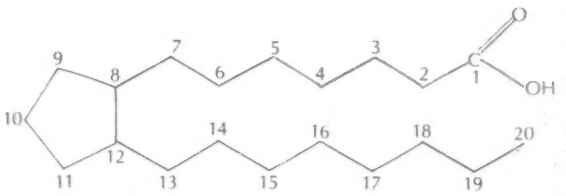


Figure 1. Among the primary prostaglandins are PGE_1, PGE_2, and $PGF_{2\alpha}$, the last two having important clinical applications.

Naming Prostaglandins

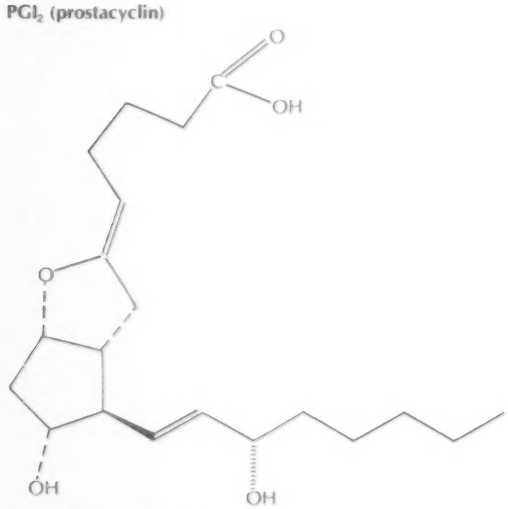
Three conventions govern the apparently complex PG nomenclature. First, the capital letter after "PG" refers to the chemical structure of the five-membered ring. Originally E stood for ether and F for phosphate buffer, indicating the substance in which the prostaglandin was more readily dissolved. Second, the subscript numeral tells how many double bonds, or unsaturated functions, are present in the two side chains of the molecule. These double bonds are normally located at the carbon atom C-13 in PG_1s; at C-5 and C-13 in PG_2s; and at C-5, C-13, and C-17 in PG_3s. Third, the Greek letter subscript α or β describes which direction in space the hydroxy groups on the side chains take relative to the plane of the ring. A hypothetical PG molecule, "prostanoic acid," illustrating the structure and numbering system of the molecule, is shown below. See Figures 1, 2, 5, and 7 for chemical formulas of most of the PGs mentioned in this issue of **Population Reports.**

"Prostanoic acid"



An early clinical investigator of the role of prostaglandins in obstetrics was Sultan M.M. Karim, then at Makerere University Medical School in Uganda. Karim reported in 1966 that he had found endogenous prostaglandins in human amniotic fluid after the spontaneous rupture of fetal membranes during labor (220). In 1968, with intravenous $PGF_{2\alpha}$, he successfully induced labor in 9 out of 10 women (233). Concurrently, Marc Bygdeman and colleagues induced labor contractions in four women with PGE_1 and in three with PGE_2 infused intravenously (70). These were the first reports on clinical effects of prostaglandins applied to the human uterus and the first deliberate use of prostaglandins in the management of human pregnancy. Soon thereafter Karim documented a correlation between blood levels of endogenous prostaglandins and frequency of uterine contractions (219)—an observation that has only recently been verified, using sophisticated fractionation methods in vitro (524).

PGI_2 (prostacyclin)



TXA_2 (thromboxane A_2)

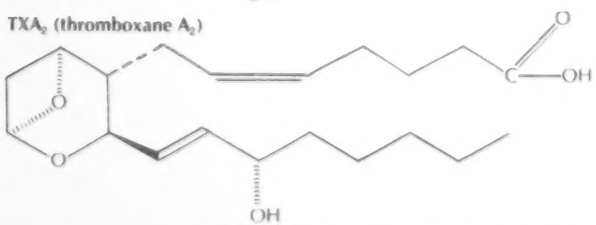


Figure 2. Related to PGs, two newly discovered classes of compounds, the prostacyclins and the thromboxanes, are powerful regulators of blood clotting.

Basic and clinical research with prostaglandins has increased in proportion to the availability of compounds for study. With increasing research, evidence has accumulated that PGs are active throughout mammalian reproductive systems. By the late 1970s, PGs were known to be involved in hypothalamic and pituitary hormone releases, ovulation, development of the corpus luteum (luteinization), regulation of the estrous cycle in domestic animals, contraction of the uterus in spontaneous abortion and labor, ejaculation, sperm transport, fertilization, and testosterone production.

In addition to their role in reproduction, PGs are involved in an extremely wide range of cellular processes. For example, in 1979 the elusive "slow reacting substance" (SRS) known to be involved in asthmatic reactions (90) was found to be related to PGs. It is a member of a newly identified family of arachidonic acid derivatives called leukotrienes; SRS is now renamed leukotriene C (332). Because of the ubiquitous activity of PGs, clinical applications currently suggested or under investigation include treatment of gastric ulcer, hypertension, asthma, peripheral vascular disease (including diabetic ulcers and Raynaud's disease), clotting disorders related to thrombosis, shock, stroke, heart attack, and keeping open the ductus in newborns until corrective surgery can be performed.

Evidence that prostaglandins could be used to stimulate labor at term and to induce abortion led in the late 1960s and early 1970s to substantial funding for research. Persistent side effects such as vomiting and diarrhea have substantially limited their use, however. Current research is focusing on practical applications of both naturally occurring PGs and various synthetic PG analogues to find the best routes of administration, the most effective doses, and the lowest incidence of side effects and to determine the relative safety of PGs used either separately or in conjunction with other labor- or abortion-inducing drugs. Drug companies have concentrated on developing new analogues and new delivery systems, such as suppositories and Silastic vaginal inserts. The World Health Organization, which established a Task Force on the Use of Prostaglandins for the Regulation of Fertility in 1972, is gathering clinical data from comparative international trials on different routes of PG administration for first and second trimester abortion and for cervical priming before vacuum aspiration (489).

Current Use

The first PGs approved for clinical use were $PGF_{2\alpha}$ and PGE_2; they were first marketed in the United Kingdom in 1972 for induction of labor (administered intravenously and extraam-

niotically) and for therapeutic abortion (administered extra-amniotically) (412). The following year use of $PGF_{2\alpha}$ was authorized in the US for second trimester abortion by intra-amniotic instillation. PGE_2 in the form of tablets was approved in the UK in 1975 for induction of labor, and PGE_2 in the form of vaginal suppositories was introduced in the US in 1977 for second trimester abortion, missed abortion, intrauterine death up to 28 weeks gestation, and hydatidiform mole. These drugs can be obtained only through hospital pharmacies and research institutions. Since 1973 $PGF_{2\alpha}$ has been registered by the Upjohn Company — that is, submitted to and approved by the appropriate government licensing agency — in 25 countries including Australia, Canada, New Zealand, South Africa, Switzerland, Taiwan, and West Germany. PGE_2 is registered by Upjohn in 15 countries including Australia, Belgium, Canada, the UK, Guatemala, Hong Kong, and Mexico. Registration does not necessarily mean that the product is currently marketed in the area, however (10). The ONO Pharmaceutical Company of Japan markets $PGF_{2\alpha}$ in Japan for intravenous and extraamniotic use and also in Korea, Taiwan, and Brazil, and PGE_2 in the form of tablets for oral use in Japan and also in Korea and Taiwan (449). (See Table 1.)

Synthetic derivatives, or analogues, of the natural PGs have been used in clinical research since 1972, when pilot studies with 15-methyl-$PGF_{2\alpha}$ and 15-methyl-PGE_2 were first reported (62, 231, 245). These analogues incorporate chemical variations of the natural PGs that prolong PG activity in the body by blocking the action of metabolizing enzymes. This permits lower or less frequent doses. Furthermore, the analogues can be injected intramuscularly or infused intravenously, whereas the parent compounds — $PGF_{2\alpha}$ especially — would cause local pain and redness. In 1979, 15-methyl-$PGF_{2\alpha}$ was licensed in the US and India.

Several newer PG analogues are being evaluated clinically. A PGE_2 derivative called sulprostone, developed by Pfizer Incorporated, USA, and Schering AG, Berlin, has been tested extensively for cervical dilation and induction of abortion. It can be injected intramuscularly. Even without premedication against side effects, almost no women experience fever or diarrhea, and the incidence of vomiting is low. Clinical tests are nearly complete enough to permit an application for marketing in West Germany (387). A PGE_1 analogue in the form of vaginal suppositories has been tested for abortion in Japan by ONO

Table 1. Characteristics and Applications of Major Prostaglandins

Name	Major Uses[1]	Common Routes[2]	Potency Relative to $PGF_{2\alpha}$	Manufacturer and Brand Name	Where Registered
$PGF_{2\alpha}$	2nd trimester abortion Labor induction	IA, IV, EA IV	1	Upjohn "Prostin F2 Alpha"	25 countries worldwide, including Australia, Brazil, Mexico, UK, US
				ONO "Prostarmon-F" ONO "Prostaglan"	Japan, Korea, Taiwan Brazil
15-methyl-$PGF_{2\alpha}$ (tromethamine salt)	1st & 2nd trimester abortion Intrauterine death *To stop postpartum bleeding*	IA, IM, VL IM *IM*	10	Upjohn "Prostin/15M"	India, US
15-methyl-$PGF_{2\alpha}$, methyl ester	*1st & 2nd trimester abortion* *Cervical dilatation before 1st trimester abortion*	*S, D* *S*	100	Upjohn	
PGE_2	2nd trimester abortion Intrauterine death & mole Labor induction *Cervical dilatation before labor induction*	S S OT, *VT* *EA, OT, VT, EG*	10	Upjohn "Prostin E2"	15 countries worldwide (Europe, Western Hemisphere, Pacific), including Guatemala, Hong Kong, UK, US)
				ONO "Prostarmon-E"	Japan, Korea, Taiwan
				Upjohn UK "Prostin E2" (OT)	UK
16,16-dimethyl-PGE_2	*1st trimester abortion* *Cervical dilatation before 1st trimester abortion*	S S	100	Upjohn Canada	
16-phenoxy-ω-tetranor-PGE_2 methyl sulfonylamide (sulprostone)	*1st & 2nd trimester abortion* *Cervical dilatation before 1st trimester abortion*	*IV, IM, EA* *IM, IC*	100	Schering AG	
16,16-dimethyl-trans-Δ^2-PGE_1 methyl ester (ONO-802)	*1st & 2nd trimester abortion*	*S, EA*	100	ONO	
9-deoxo-16,16-dimethyl-9-methylene-PGE_2	*2nd trimester abortion*	S	15	Upjohn	

[1]Uses and routes approved by at least one national drug regulatory agency appear in roman type, experimental uses, in italic type.
[2]EA = extraamniotic; IA = intraamniotic; IM = intramuscular; IV = intravenous; S = vaginal suppository; D = vaginal device; OT = oral tablet; VT = oral tablet administered vaginally; VL = vaginal liquid; IC = intracervical; EG = endocervical gel.

Pharmaceutical Company. Side effect rates are considerably lower than those caused by currently available PGs. This derivative may be submitted to the Japanese health ministry for licensing in 1980 (449). Development of another PGE derivative, 9-deoxo-16,16-dimethyl-9-methylene-PGE_2, has recently been announced by the Upjohn Company, USA. Reportedly it is more stable than PGE_2, and its effects are more specific to the uterus. Preliminary clinical trials show that it is effective for early and midtrimester abortion by several routes of administration and for cervical dilatation with reduced gastrointestinal side effects (66, 462). Finally, some progress has been made in synthesizing PG derivatives with heightened luteolytic activity in animals, that is, the ability to block progesterone production by the corpus luteum. These compounds have not yet been tested in women, who have not shown the luteolytic effects of PGs that are commonly observed in lower species. (See "Mode of Action," below, and "New Derivatives," pp. G-107–110.)

MODE OF ACTION

Basically, PGs function like hormones, regulating a vast array of physiologic processes. Unlike hormones as classically defined, however, PGs are made on demand and are released by unspecialized cells. Naturally occurring PGs usually act within the cell or organ where they are released. They are deactivated instantaneously, generally without a measurable increase in the level of PG circulating in the blood. Because of this local action, PGs resemble the intracellular messenger molecule cyclic-3',5'-adenosine monophosphate (cyclic AMP, or cAMP). In fact, PGs act on many of their target cells — for example, corpus luteum cells — by joining with the appropriate cell membrane receptor molecule to produce an increase in cAMP (439). In other target tissues — for instance, the myometrium, or uterine muscle — PGs act by causing the release of calcium ions into the cell (77).

The role that PGs play in mammalian reproduction is still not entirely clear, but to date at least three different functions have been identified by which PGs may affect pregnancy. These are:

(1) as a smooth muscle stimulant, acting directly and/or indirectly on the myometrium, causing it to contract.
(2) as a cervical primer, changing the structure of the cervix to hasten the process known as cervical ripening.
(3) as a luteolytic agent (luteolysin), inhibiting the ability of the corpus luteum to secrete the female hormone progesterone, which is necessary to maintain pregnancy. This effect has been observed in many mammals but not in humans.

The first two functions have important clinical applications not only for first or second trimester abortion but also for assuring safe delivery at term, for treating various complications of pregnancy, and perhaps eventually for understanding and treating a wide range of menstrual and reproductive disorders.

Stimulating Uterine Contractions

The role of PGs in stimulating the uterine muscle was one of the first to be discovered (163, 256) and today forms the basis for the principal clinical applications of PGs.

The natural PGs PGE_2 and $PGF_{2\alpha}$ and all currently available analogues act on the uterus, whether in initiating labor, abortion, or even menstrual cramps, by stimulating the muscle tissue, or myometrium. Despite contradictory reports from very early work on PGs, the current consensus is that $PGF_{2\alpha}$ stimulates the uterus in all conditions, whether pregnant or not, at any stage of pregnancy, in vitro or in vivo. On the other hand, PGE_2, which during pregnancy is about five times as potent a uterine stimulant as $PGF_{2\alpha}$, in vitro relaxes tissue from a nonpregnant uterus (148). In fact, PGE_2 reverses the contractile effect of $PGF_{2\alpha}$ under certain conditions — for example, in an isolated myometrium from a nonpregnant woman (60, 382) or during normal menstruation (301, 302).

The biochemical basis for this direct action of PGs on the uterine muscle is still being explored. There are many PG receptors on the sarcoplasmic reticulum of the myometrium, that is, the intracellular membrane responsible both for conducting the signal to contract to the myometrial fibers and for initiating the contraction itself (78). PGE_2 and $PGF_{2\alpha}$ cause this membrane to release bound calcium ions into the cell fluid. These calcium ions in turn trigger contraction of the muscle fibers (77). Unlike oxytocin, which can stimulate the uterus only when pregnancy is near term, PGs can promote calcium release in either the pregnant or the nonpregnant myometrium. In this role as a muscle stimulant, PGs have an opposite effect from progesterone since progesterone encourages the sarcoplasmic reticulum to retain calcium, thus quieting uterine activity (76).

PGs may act elsewhere in the uterus. For example, they probably constrict blood vessels sufficiently to account for part of the discomfort of dysmenorrhea (see pp. G-103–105). Arpad I. Csapo has suggested that constriction of the uterine and placental blood vessels is one of the first events in the abortion process. Since he believes that the uterine muscle is at first unresponsive to stimulants like oxytocin or PGs, he hypothesizes that administering PGs causes an acute vasoconstriction, cutting off the blood supply to the placenta ("prostaglandin impact") (110). This, in turn, according to Csapo, reduces the progesterone supply ("progesterone withdrawal") enough to make the myometrium receptive to PGs, exogenous or endogenous, so that it will start contracting regularly (110). Clinical observations (114, 115) and data from PG assays during abortion (174) suggest that endogenous PG production may be necessary to continue the abortion process, supplementing the exogenous PG dose.

Another newly discovered class of PGs, the prostacyclins (PGIs), also acts on the myometrium, although, as with other PGs, some of the emerging reports are contradictory. Most initial reports show that prostacyclin (PGI_2) applied in vitro relaxes both the pregnant and nonpregnant human myometrium (342, 382). In one study, PGI_2 counteracted contractions evoked by $PGF_{2\alpha}$ (345). Another study described a biphasic effect of PGI_2 — an initial stimulation followed by relaxation (345). A third study found that PGI_2 stimulated uterine contractions (483). Some of these differences may have occurred because laboratories use different incubation media, with different calcium concentrations. In any case, the discovery of the prostacyclins and their uterine-regulating potential has opened new opportunities for PG research.

Priming the Cervix

The most recently identified role of prostaglandins in reproduction is their role in softening and dilating the cervix, sometimes referred to as "cervical priming" or "ripening." At first, many investigators assumed that PG-induced uterine contractions indirectly dilated the cervix (292, 293). More recently it has become evident that PGs, especially PGE_2, also specifically alter the structure of the connective tissue of the cervix. Several

PG analogues are capable of dilating the pregnant cervix in 6 to 12 hours. This finding suggests that PGs, PG analogues, and conversely also PG inhibitors may soon play a much larger role in the management of pregnancy, abortion, and labor.

The human cervix is a barrel-shaped organ. Its function during pregnancy is to remain tightly closed, then in labor to become effaced, or flattened, so that the shape of the internal os and cervical canal is lost, and finally during delivery to dilate at the external os so that the fetus can be expelled (see Figure 2). The bulk of the cervix consists of connective tissue — protein collagen fibers, smaller reticulum fibers, their mucopolysaccharide sheaths, and a gellike interstitial substance, or matrix. During the course of pregnancy the proportion of gel to collagen fiber increases, the reticulum fibers align with the collagen fibers, and the water content of the gel increases slightly (48). As delivery approaches, the collagen fibers dissociate and branch out like a rope fraying (48). New synthesis of glycosaminoglycan (mucopolysaccharide) and a significant loss of the protein content of the collagen also have been observed (120). Thus, the early concepts of the cervix as a sphincter, as merely an elastic girdle responding to contractions of the uterine body, or as a sponge absorbing more water at dilation are inaccurate. The structure of the cervix itself actively changes during dilation.

Current research implicates PGs in these processes. Unlike oxytocin, $PGF_{2\alpha}$ and PGE_2 actually decrease cervical stiffness (stretch modulus, a measure of resistance to stretching) when added to portions of human cervical tissue in vitro (507). For women whose labor was induced by oral PGE_2, the stretch modulus of connective tissue from the cervix (measured in vitro) was about half that of tissue from women whose labor was spontaneous or induced by oxytocin (99). Preliminary studies with the nonpregnant cervix in vitro suggest that arachidonic acid, a PG precursor, or its metabolites may stimulate collagen breakdown during cervical ripening (198, 475). A study on sheep provides direct evidence that endogenous PGE synthesis increases in the cervix during labor to effect cervical dilation and softening. The PGE production rate, measured in vitro by radioimmunoassay, was fourfold higher at delivery than in late pregnancy (146).

PGs are now being used for cervical priming at the time of delivery and before induced abortion. Natural PGs have been used much more often to induce labor, and PG analogues, in early abortion. Endocervical gels and suppositories as well as intramuscular and intracervical injections are being developed and improved for this new clinical use of PGs.

Luteolysis

By far the most tantalizing function of PGs in the domain of human reproduction, from both the theoretical and clinical viewpoints, is as a luteolytic agent, or luteolysin — that is, an agent which can prevent the corpus luteum of the ovary from secreting progesterone. This progesterone is necessary to prepare the uterus for implantation of a fertilized egg and to maintain pregnancy until about the ninth week, when the placenta gradually takes over this function (113, 117, 329, 450). Therefore, any interruption in the production of progesterone by the corpus luteum can interrupt early pregnancy.

Do PGs prevent the corpus luteum from producing progesterone? To date the answer is "yes" in some animals but "not proven clinically" in human females.

Since 1969, when Bruce Pharriss and colleagues reported that $PGF_{2\alpha}$ caused luteolysis in the rat (352), several lines of evidence have accumulated indicating that $PGF_{2\alpha}$ is a luteolysin in most laboratory and domestic animals. For example, (1) administration of $PGF_{2\alpha}$ causes luteolysis in cows, gerbils, hamsters, guinea pigs, horses, mice, monkeys, pigs, rabbits, and rats; (2) at the time of luteolysis higher levels of $PGF_{2\alpha}$ are found in the blood of sheep, pigs, cows, and guinea pigs; (3) administration of PG synthesis inhibitors prevents luteolysis in guinea pigs, rabbits, and rats; and (4) immunization against $PGF_{2\alpha}$ prolongs the life span of the corpus luteum in guinea pigs and sheep (203).

The precise mechanism by which $PGF_{2\alpha}$ causes the corpus luteum to stop secreting progesterone and to regress in these animals is not known. A once popular theory that $PGF_{2\alpha}$ acts indirectly, by restricting ovarian blood circulation, has been disproved in several animals (47, 209, 246). Blood flow is in fact reduced, but after progesterone secretion has diminished (348). Current evidence suggests that $PGF_{2\alpha}$ acts directly on luteal tissue; this conclusion is based on tissue culture experiments with rats (121), rabbits (336), hamsters (14), monkeys (94), pigs, and cows (191). Some studies suggest that $PGF_{2\alpha}$ may affect luteal function by acting on cyclic AMP, which serves as a mediator of PG action in many target tissues (439). Another

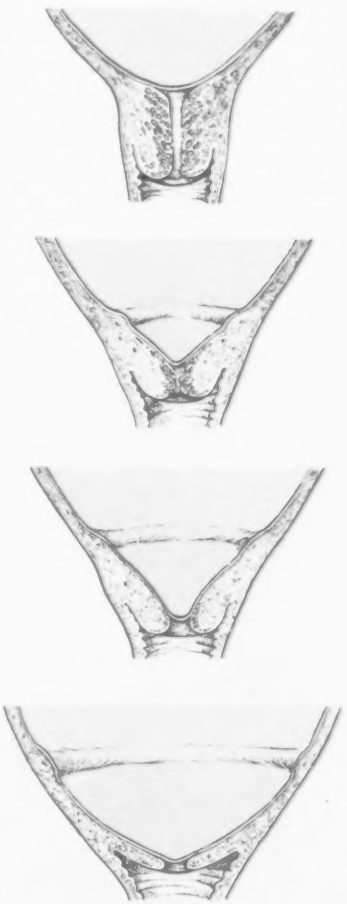


Figure 3. During labor the cervix changes physical shape, in part because of uterine contractions and the pressure of the fetal head upon it and in part because of changes in the consistency of cervical tissue. PGs can hasten these changes. The nulliparous cervix, at the end of pregnancy, is shown at top. During labor the cervix becomes increasingly effaced (second and third drawings). As delivery approaches, the cervical canal disappears entirely (bottom).

Source: adapted from Hellman et al. (512)

Prostaglandins in Male Reproductive Physiology

Prostaglandins were named for the prostate gland because they were discovered in semen and assumed to originate in that gland. Nevertheless, the role of PGs in male reproduction has not received as much attention as their role in female reproduction.

The major PGs in human semen are 19-hydroxy-PGE_1 and 19-hydroxy-PGE_2; their levels are about four times those of PGE_1 and PGE_2 (213, 429). These 19-hydroxy-PGs primarily inhibit uterine activity rather than stimulate it, as PGE_1 and PGE_2 do (374). This finding confirms previous observations that human semen relaxes myometrium in vitro and the uterus when deposited intravaginally (144, 145).

A variety of findings show that PGs may play some role in male fertility and thus may warrant further attention:

- In a group of men with otherwise unexplained infertility, seminal PG levels were lower than normal (64); in another small series, infertile men had significantly depressed levels of 19-hydroxy-PGEs (286).
- A group of infertile men with normal sperm counts did not show significantly lower PG levels compared with fertile men with similar sperm counts, but men with abnormally high sperm counts (9 of 10 of them infertile) had 19-hydroxy-PG levels in their seminal plasma significantly lower than normal (237).
- Exogenous male hormones elevate hydroxy-PG levels in semen (406) and improve sperm motility (46). Thus it has been suggested that androgen treatment might improve fertility in men with low hydroxy-PG levels, which can easily be monitored by thin-layer chromatography (285).
- Aspirin, a PG synthesis inhibitor, lowers the PG content of semen (97), but the consequent effects of PG synthesis inhibitors on fertility have not been fully examined.
- By means of gas chromatography–mass spectrometry, prostaglandins and their metabolites in human prostate gland have been quantified. Since PGs are synthesized and degraded in this tissue, they probably have a physiological role in the prostate (100).

The significance of these findings for theoretical understanding of male fertility—whether these PGs have a role in sperm activation or transport in the female reproductive tract—remains to be clarified. So does their practical application to the management of male infertility.

possibility is that $PGF_{2\alpha}$ acts by altering calcium flux within the luteal cell membrane (14).

In women, however, administration of exogenous prostaglandins apparently does not cause the corpus luteum to regress. Most early attempts to induce luteolysis with PGE_2 and $PGF_{2\alpha}$, generally in the mid or late luteal phase of the menstrual cycle in nonpregnant women, were unsuccessful (36, 195, 211, 212, 214, 278, 282, 444). Some investigators observed a decline in progesterone, but it was transient (107, 143, 281, 451, 480).

Yet many are reluctant to concede that the luteolytic effect of PGs clearly seen in animals is totally absent in humans. Indeed, there is reason to expect that PGs will be shown to act somehow, perhaps through an indirect mechanism, on the human corpus luteum so as to inhibit or reduce progesterone secretion. Some of the steps in this process have already been identified. First, the necessary anatomical connection between the uterus and ovary, a tortuous overlapping of uterine veins on the ovarian arteries, has been identifed in human specimens (16) as well as in cows, hamsters, rats, and sheep (203). Second, $PGF_{2\alpha}$ receptors have been discovered in the cell membranes of the human corpus luteum (359, 365), a prerequisite if $PGF_{2\alpha}$ is to act on target cells in the corpus luteum; one group reported a change in the dissociation constant, a measure of the affinity of this receptor for the PG, after abortion by vacuum aspiration (359). Third, another fine point in the luteolytic mechanism well documented in animal experiments has now been observed in human luteal tissue: in human granulosa cells (precursors to luteal cells) cultured in vitro, $PGF_{2\alpha}$ does reduce progesterone release (325). Fourth, some have speculated that $PGF_{2\alpha}$ does have a luteolytic effect in women but that it acts only within the ovary and not when administered systemically. In one experiment, exogenous $PGF_{2\alpha}$ was injected directly into the ovary and produced luteolysis (248). Fifth and finally, measurements show elevated amounts of endogenous $PGF_{2\alpha}$ in ovarian venous blood at the time of luteolysis (2). These data and speculations keep alive the possibility that in the future PGs could be used to regulate human luteal activity, although the effect will probably not be as direct as was once expected.

The search for a measurable luteolytic effect continues. For example, in recent tests three days before expected menstruation 16 normally cycling women took 2.0 or 3.0 mg of 15-methyl-$PGF_{2\alpha}$ methyl ester in a single vaginal suppository for a total of 35 cycles. Among these women eight pregnancies were subsequently documented by radioimmunologic hCG pregnancy tests. As expected from previous research, in women who were not pregnant there was no change in progesterone levels, although these women had some spotting and cramps. Their menses occurred on schedule. In the eight women later found to have been pregnant, however, heavy bleeding began within hours and levels of human chorionic gonadotropin (hCG) dropped from the high readings characteristic of pregnancy (242). It is not possible to determine from this evidence whether uterine contractions disrupted the placenta, cutting off that source of progesterone, or whether the PG had a luteolytic effect in women newly pregnant but not in nonpregnant women about to menstruate.

These clinical results are comparable to those reported when other PGs were used in larger doses to terminate confirmed early pregnancies (see p. G-90). In studies of early abortion, women who aborted completely experienced a drop in progesterone to about 35 to 50 percent of initial values in 24 hours, then to about 10 percent in one week (103, 316, 318, 370). These studies leave open the possibility that some luteolytic action occurs when PGs are administered to a pregnant woman.

INDUCTION OF LABOR

For more than a decade, PGs have been used on an experimental basis to induce labor. In this use, the action of PGs in stimulating uterine contractions is paramount. The route ini-

tially tested by Karim in Uganda in 1968 was intravenous (224, 233). Extraamniotic and oral administration and vaginal gels and tablets followed. Although both $PGF_{2\alpha}$ and PGE_2 have been tested in clinical trials, PGE_2 is now preferred because of its cervical priming action. The synthetic PG analogues generally have not been employed to induce labor since there is no information about their effects on the fetus.

PGE and $PGF_{2\alpha}$ administered intravenously for induction of labor were approved in the United Kingdom in 1972. In 1975 stable 0.5 mg oral tablets of PGE_2 also were approved in the UK. In the US the use of prostaglandins to induce labor, that is, as an oxytocic, has not yet been authorized by the Food and Drug Administration.

Medical practices with respect to induction of labor differ in the US and Europe. In the US, induction of labor is permitted only for medical reasons; intravenous oxytocin infusion allows close monitoring and permits an immediate halt to administration if contractions become too strong or fetal distress develops. In Europe induction of labor is more common. Thus much of the research on PGs for induction of labor has been undertaken in the UK.

Whether induction is planned for maternal or fetal indications, PGs now offer an alternative to the standard technique of artificial rupture of the membranes (amniotomy) and intravenous infusion of oxytocin. Although it is difficult to compare inductions of labor by PGs and by oxytocin because of differences in the selection of subjects, dose schedules, treatment protocols, and criteria for success, both $PGF_{2\alpha}$ and PGE_2 are considered to be as effective as oxytocin in inducing uterine contractions at term (6).

With respect to side effects and ease of administration, each method and route has advantages and disadvantages for specific women and in particular medical environments. In general, the advantages of PGs are: they do not require intravenous infusion; they do not contribute to excess water retention, which is a special problem for women with eclampsia, hypertension, or heart or kidney disease; and they help to ripen the cervix. On the other hand, compared with oxytocin, PGs have the disadvantage of a much narrower dosage margin. There is only a narrow range of doses that are effective without causing excessive gastrointestinal side effects — diarrhea, nausea, and vomiting — and possibly overstimulating the uterus and adversely affecting fetal circulation (70, 437). The thrust of current clinical research on PGs, therefore, is to develop routes of administration and procedures that minimize this disadvantage, that are acceptable to women in labor, and that are easily utilized by medical or paramedical personnel.

Comparing Intravenous PGs and Oxytocin

Since obstetricians were accustomed to administering oxytocin intravenously, the first clinical trials of $PGF_{2\alpha}$ and PGE_2 to induce labor at term also utilized this route (224, 233). With PGE_2, the effective dose range is about 0.5 μg per minute, increasing to about 2.0 μg (147, 224); the effective therapeutic range for $PGF_{2\alpha}$ is 5 to 20 μg per minute (148). (This can be compared with the usual infusion of oxytocin at about 2 mU/minute, adding to or doubling the dose every 30 or 60 minutes until regular labor contractions are established.)

Mean induction-to-delivery intervals with intravenous PGE_2 range from 2.6 hours in multiparas having elective inductions (418) to 9.25 hours in women with unripe cervices and medical indications for induction (205). Primiparas average two to three hours longer than multiparas. These intervals are comparable to those observed with oxytocin (404).

The qualitative and quantitative characteristics of uterine contractions induced by PGs differ very little from those displayed in spontaneous or in oxytocin-induced labor. Both the amplitudes and the frequencies of contractions are in the same ranges, and the shapes of the recorded curves are comparable. Clinically, PG-induced contractions are considered indistinguishable from spontaneous contractions.

In comparison with oxytocin, which is effective at intravenous doses ranging from 2 to 32 or more mU per minute, $PGF_{2\alpha}$ has a narrower range of dose response: only four- or fivefold increases in dose are tolerated. Because there is such a narrow margin of tolerance between the threshold of desired uterine activity and overactivity, PGs are more difficult to manage than oxytocin. If uterine pressure surpasses 12 mm of mercury between contractions without a return to resting tone, hypertonus, or excess tension, has developed. Hypertonus may impair placental blood flow and cause the fetal heartbeat to slow down (bradycardia), possibly resulting in a depressed, oxygen-starved baby. Fetal heart rate anomalies associated with hypertonus have been reported in 3.6 and 5.5 percent of women receiving intravenous PGE_2 and $PGF_{2\alpha}$, respectively (433, 437) (see Table 2). Resulting fetal distress is probably less common, its reported frequency depending on the criteria used.

At first PGs seemed to produce hypertonus more often than oxytocin did, especially if they were infused intravenously (70, 437). More recent research casts doubt on this conclusion. Comparing the results of 2,834 spontaneous, oxytocin-induced, oxytocin-augmented, and oral PGE_2-induced labors, Emanuel A. Freidman and Marlene R. Sachtleben found higher rates of abnormal contractions with each of the three oxytocic regimens than in spontaneous labor. Moderate to severe variable slowing of the fetal heart rate occurred significantly more often with oxytocin augmentation than in normal labor, but was not more frequent with PGE_2. Moderate to severe late slowing of fetal heart rate occurred significantly *less* often with PGE_2 than in normal labor when the associated uterine contractions were normal or sustained (tetanic) (152).

Anesthesia may aggravate the effect of PGs on the uterus. Michel Thiery and colleagues recorded several times as many incidents of uterine hyperactivity and fetal bradycardia in groups of women given continuous epidural anesthesia (injections of local anesthetic into the lumbar spine above the dura membrane) as in matched controls also induced by amniotomy and intravenous PGE_2 or $PGF_{2\alpha}$ but without anesthesia (435). Since hypertonus was sometimes seen immediately after a dose of anesthetic, the researchers suggested that anesthesia in combination with PGs may overstimulate the uterus. Furthermore, they documented fetal heart rate anomalies alone, without associated uterine hypertonus, and noted that fetal scalp pH, one measure of fetal distress, was significantly lower (more acid) on the average in the anesthetized groups. They recommended that local or regional anesthesia not be administered during PG-induced labor except with very close monitoring (435).

A further disadvantage of PGs in inducing labor is side effects, although these are being reduced with new vaginal delivery systems. PGs may cause gastrointestinal disturbances, usually in the form of occasional vomiting. Clinically, this provides a safety factor, since nausea usually precedes uterine hyper-

tonus, but of course vomiting makes PGs less acceptable to women. The incidence of gastrointestinal side effects ranges from 4 to 20 percent during intravenous infusion (433, 437) (see Table 2). Side effects are more frequent in primigravidas and in women with unfavorable cervices, who need higher doses of PGs to initiate effective labor.

Oral Administration

The development of a stable tablet for oral use represents an important gain in acceptability for the woman and in ease of management for medical personnel. In most studies, however, oral administration appears to be slightly less effective than intravenous or vaginal administration (see Table 2).

PGE_2 was originally administered orally in aqueous solution, an effective but bitter-tasting drug. It was inconvenient for medical personnel to use since the unstable PGE_2 had to be prepared fresh. Since 1975, stable 0.5 mg tablets for oral use have been available in the United Kingdom (10). Oral doses are taken at 30 to 60 minute intervals, starting with a single tablet and gradually increasing to a maximum of four tablets (2.0 mg) at a time. Plasma levels of the first PGE_2 metabolite, 15-keto-PGE_2, reach peak values 45 minutes after ingestion, establishing this dose rate as appropriate (165).

The incidence of gastrointestinal side effects ranges from 2 (190) to 55 percent (273), but usually amounts to 10 percent or less. There are fewer complaints with the tablets than with PGE_2 solution (140).

With oral tablets, vomiting reduces the likelihood of successful induction and lengthens delivery intervals, particularly in primigravidas who need higher doses, because vomiting produces a wide variation among individuals in absorption of the PG. Vomiting may serve as a warning that increased doses would produce hypertonus. Hypertonus and fetal distress appear to be less frequent with oral tablets than with intravenous administration (see Table 2).

A recent retrospective study in Great Britain of 144 routine inductions of labor with the 0.5 mg PGE_2 tablets showed that multiparas were more often successful than primiparas. Success clearly depended on the dose and the side effect rate. The 36 percent who did not achieve prompt delivery included 15 percent who had to withdraw because of gastrointestinal side effects and 6 percent whose contractions faded after they vomited. To limit side effects, the clinicians conducting this study recommended not exceeding a dose rate of 1.0 mg per hour, a

Table 2. Labor Induction with Prostaglandins, by Route of Administration and Type of PG, Selected Studies, 1972-1979

Author & Date	Ref. No.	No. of Women	Selection Criteria	Dosage	Other Techniques Used	Effectiveness (%)	Mean Hours Induction to Delivery (Nullip./Parous)	Maternal Side Effects (%)[a]	Uterine Hypertonus/Fetal Heart Rate Anomalies (%)	Cesarean Section Required (%)
Intravenous/PGE_2										
Thiery et al. 1975	437	55	elective	initially 0.1 μg/minute, doubled every 30 minutes to maximum 3 μg/minute	initial amniotomy, no anesthesia	100	5.8/3.3	V: 20	NR/3.6[b]	1.8
Thiery et al. 1977	435	53	elective	initially 0.2 μg/minute, doubled every 30 minutes to maximum 2 μg/minute	initial amniotomy, epidural block with bupivacaine	100	5.9/4.5	V: 13.2	47/13	1.7
Intravenous/$PGF_{2\alpha}$										
Thiery et al. 1977	435	64	elective	initially 2 μg/minute, doubled every 30 minutes to maximum 30 μg/minute	initial amniotomy, epidural block with bupivacaine	97	7.1/4.1	V: 16.7	29/10.9	1.7
Oral[c]/PGE_2										
Ang et al. 1978	7	153	medically indicated	0.5 mg/hour × 4, then 1.0 or 1.5 mg/hour	initial amniotomy	91	8.1	GI: 9.2	NR	3.9
Elder & Stone 1975	141	91	medically indicated, mainly post-maturity or hypertension	0.5 mg/hour × 2, then 1.0 mg/hour × 2, then 1.5 mg/hour	initial amniotomy	91	11.2/7.5	GI: 15	0/0	3.3
Gordon-Wright et al. 1979	167	80		0.5 mg/hour × 2, then 1.0 mg/hour × 2, then 1.5 mg/hour	initial amniotomy	66	6.8	GI: 15	3.8/0	9

NR = not reported

[a]V = vomiting; GI = gastrointestinal; D = diarrhea
[b]Hypertonus and fetal heart rate anomalies; one fetal death due to heart defect.
[c]Oral tablets except as noted
[d]Oral gelatin capsules

(continued on next page)

policy that would discourage the use of this method for women delivering for the first time (167).

In centers where nursing staff, intravenous infusion pumps, and electronic monitors are in limited supply, the oral PGE_2 tablets have provided a safe and convenient alternative to intravenous infusion of oxytocin (7, 157, 448, 497). Uterine activity and fetal condition were assessed frequently, and if any signs of fetal distress appeared, monitoring of labor began. In this way the majority of these PG-induced labors were managed without the amount of staff attention needed for intravenous infusion or continuous fetal monitoring. Even where inducing labor by intravenous oxytocin is the rule, both the nursing staff and the women in labor have appreciated the freedom from infusion pumps that oral PGE_2 tablets afford (167, 331). (In Scandinavia, oxytocin is also administered by nasal spray or sublingually — that is, under the tongue — to provide the same freedom of movement (151). Trained midwives adhere strictly to a gradually escalating dose protocol because, when administered by these routes, oxytocin absorption is variable, and the dose cannot be regulated once it is administered. The same precautions need to be taken with PGE_2 given by oral or vaginal routes.)

Avoiding the immobility required for intravenous infusion and bedside fetal monitoring may actually hasten delivery. Using a newly developed telemetry device for remote reading of fetal heart rate and uterine activity, West German researchers monitored 35 women in whom labor was induced by oral PGE_2 tablets and compared them with 40 similar women monitored while lying in hospital beds (416). The women with the device were allowed to move, sit, stand, and walk around freely (416). Compared with the women immobilized in bed, these women needed less analgesia and fewer PGE_2 tablets, took less time to deliver, and their infants had slightly higher mean blood pH and Apgar scores (rapid assessments of newborns' clinical condition based on a combination of factors). The better results were attributed to the opportunity to maintain an upright posture, which assists the woman in labor and allows gravity to hasten fetal expulsion (510).

Vaginal Tablets and Suppositories

The 0.5 mg oral tablets have been used vaginally on an experimental basis to induce labor. This route of administration has not been approved in the US or the UK. PGE_2 suppositories for vaginal use are made by hospital pharmacies for research purposes and have not been marketed by any drug companies to

Table 2. (Continued)

Author & Date	Ref. No.	No. of Women	Selection Criteria	Dosage	Other Techniques Used	Effectiveness (%)	Mean Hours Induction to Delivery (Nullip./ Parous)	Maternal Side Effects (%)[a]	Uterine Hypertonus/ Fetal Heart Rate Anomalies (%)	Cesarean Section Required (%)
Gordon-Wright et al. 1979 (continued)		36		0.5 mg/hour × 2, then 1.0 mg/hour × 2, then 1.5 mg/hour	no amniotomy	53	10.9	NR	0/2.7	11
		28	to augment labor	0.5 mg/hour × 2, then 1.0 mg/hour × 2, then 1.5 mg/hour		71	7.3	NR	NR	0
Karim & Sharma 1972[d]	230	1,000	almost all medically indicated	initially 0.5 mg, increasing in 0.5 mg steps up to 2.0 mg per application, given at 2-hour intervals (for maximum 48 hours) until adequate uterine stimulation or 6 cm cervical dilation achieved	amniotomy at 6 cm dilation	90	NR	V: 6.5 D: 3.4	NR	6.1
Thiery et al. 1974	436	50	elective	0.5 to 1 mg every 2 hours	initial amniotomy, no anesthesia	98	6.8/4.4	V: 23.4	0/0	0
Vaginal tablets/PGE_2										
Gordon-Wright & Elder 1979	168	505	medically indicated	single dose: 1 mg 2 mg 3 mg 4 mg 5 mg	no amniotomy	34 41 57 70 63	10.8 6.6 7.7 6.4 8.1	none	0/0	NR
Vaginal suppositories/PGE_2										
Shepherd et al. 1979	401	352	medically indicated, favorable cervix	3 mg, single	amniotomy after labor established	100	12.5/7.2	NR	0.3/0	4.8
		150	as above but unfavorable cervix		as above, plus one or two 3 mg PGE_2 priming doses	95	16.0/10.0	NR	0/0	20.7

date. Experience with these methods in the UK is limited but promising.

One large study has applied the 0.5 mg PGE_2 tablets intravaginally, either alone or with other procedures. In London, initial research on a small group of women found that the 15-keto metabolite of PGE_2 climbed to peak plasma levels in about three hours, although the levels did not appear to be clearly dose-related (168). Then, clinical trials were expanded to include 505 women from two different hospital populations. They received single doses of 1, 2, 3, 4, or 5 mg PGE_2 in tablets without prior amniotomy. Within comparable groups, success rates were proportional to dose, ranging from 34 percent in the 1 mg group to 70 percent in the 4 mg group. Neither gastrointestinal side effects nor uterine hypertonus was observed among these women, even though the single dose was higher than that generally used orally. The researchers noted that this method was more effective than intravenous oxytocin alone, more acceptable to laboring women, and more convenient for the attending staff than combining amniotomy with oxytocin, even though the combined amniotomy/oxytocin procedure was more effective than PGE_2 alone (168).

Another large study of labor inductions used 3 mg PGE_2 vaginal suppositories. The treatment protocol called for a 3 mg vaginal suppository immediately upon hospital admission, the evening before formal induction, for women with a poor prognosis for labor. The following morning all women, regardless of prognosis, received a 3 mg suppository, followed by amniotomy after regular contractions developed. The overall effectiveness rate was 98 percent. Induction-to-delivery times ranged from 16.0 hours (counting from the second, inducing dose) in primigravidas with poor prognosis to 7.2 hours in multigravidas with favorable prognosis. In primiparas with poor prognosis, adding the priming dose the evening before induction cut the cesarean section rate from 42 to 21 percent (401).

While all of these formulations and routes are still being tested, the evidence available suggests that prostaglandins, especially PGE_2, can play an important role in the induction of labor. Gastrointestinal side effects continue to trouble 10 or 20 percent of women, especially primiparas, but the high incidence of vomiting and diarrhea reported in early studies is now being reduced with oral and, especially, vaginal use. The most serious complication — uterine hypertonus with fetal distress — occurs less frequently as practitioners gain experience with PGs. At the same time, new attention is focusing on the use of PGs in cervical dilation, a key factor in preparing a woman for labor.

CERVICAL PRIMING

Significant improvements in the outcome of labor can be achieved by use of PGE_2 to prepare, or prime, the cervix before induction of labor. Cervical priming differs from induction of labor in that it is intended to dilate, soften, and efface the cervix without necessarily starting strong uterine contractions; by contrast, induction of labor involves administering an oxytocic, or uterine-stimulating drug, and rupturing the amniotic sac in order to initiate the physiological process by which the fetus is expelled from the uterus.

To a woman whose cervix is uneffaced, closed, and firm, low doses of PGE_2 are easily administered, the evening before induction, in the form of oral tablets, vaginal suppositories, or endocervical gels. This cervical priming procedure causes almost no discomfort and does not commit the obstetrician to formal labor induction if the cervix does not dilate sufficiently. The priming dose of PGE_2 not only makes labor less painful but also increases the likelihood of successful labor induction, shortens delivery time, reduces the number of cesarean sections, and in many cases brings on a more natural labor without the need for artificial induction. Cervical priming is also effective when induction of labor before term is indicated for medical reasons or before abortion procedures (see pp. G-93–95).

One of the most important factors affecting the success of labor induction is "inducibility" — a condition largely determined by the clinical appearance of the cervix. This is usually expressed in terms of the Bishop score, which assigns points for cervical consistency, effacement, position, dilation, and for the position of the presenting part of the fetus, on a scale of 1 to 13 (30). For example, a woman with a long, closed, firm, and uneffaced cervix would score only between 0 to 3. The Bishop score is particularly useful in primiparas for predicting the length of the first stage of labor. For example, primiparas with a Bishop score of 0 to 2 took six hours longer for cervical dilation than did primiparas with a score of 3 to 5 — a difference that was not seen in women with previous births (434).

Extraamniotic Administration

To determine the best route of administration for cervical priming, PGE_2 has been tested extraamniotically, orally, and vaginally. In several studies, PGE_2 has been administered extraamniotically in viscous gel at a priming dose of less than 1 mg. Gastrointestinal side effects have been minimal (see Table 3). The increases in Bishop scores ranged from 3.0 (75) to 4.9 points (402, 432, 485), improving the cervical status of these women from poor to favorable. These effects are comparable to those obtained with the use of laminaria (258).

Labor was often shorter than in women with similar initial Bishop scores who did not receive cervical priming treatment — in one series, 25 percent shorter (75). In one study, primigravidas with initial Bishop scores of three or less and medical indications for labor induction were in labor for an average of 10.7 hours, compared with 14.9 hours for similar controls without PGs (75). PGE_2 causes mild uterine contractions, sometimes felt as slight backache, and in these studies induced labor without further intervention in 20 (75) to 53 percent (402).

With PG priming, A.A. Calder and colleagues documented a lower incidence of depressed infants: 6.6 percent with Apgar scores of four or less versus 23 percent of untreated controls; a lower cesarean section rate: 14 percent versus 32 percent in controls; and a lower frequency of maternal fever: 4.1 percent versus 32 percent in controls (75).

A balloon catheter developed by Edward M. Southern of the Upjohn Company can combine slow mechanical dilatation, by inflation of the balloon in the cervical canal, with extraamniotic administration of PGs or other oxytocic fluids by means of a tube through the balloon. A pilot study of the device utilized a single 100 μg dose of PGE_2 in most cases, with a second dose in a few instances. In 17 women using the device for three hours, mean cervical dilation was 10.5 mm; in 43 women using the device for six hours, 12.7 mm. At this low PG dose, gastrointestinal side effects are few (410).

Table 3. Cervical Priming with Prostaglandins, Selected Recent Studies, 1977-1979

Author & Date	Ref. No.	No. of Women	Selection Criteria	Priming Agent	Route	Dosage	Increase in Bishop Score (points)	%Women in Labor during Priming	Mean Hours Induction to Delivery
Calder et al. 1977	75	121	obstetric indications	PGE_2	extraamniotic	240, 400, or 480 μg	3.0	20	10.7
		31		none			NR	NR	14.9
MacKenzie & Embrey 1979	311	48	primigravidas, medical & obstetric indications	PGE_2	vaginal gel	5 mg	8.4	69	8.6
				$PGF_{2\alpha}$	vaginal gel	25 mg	2.2	13	10.6
O'Herlihy & MacDonald 1979	337	65	primigravidas, Bishop scores 0-3, 1/3 elective	PGE_2	vaginal gel	2 mg	6.6	48	8.5
		30		placebo			0.7	0	13.9
Pearce 1977	350	25	obstetric & medical indications	PGE_2	oral tablet	0.5 mg/hour × 10	3.3	20	NR
		23		placebo			1.6	4	NR
Steiner et al. 1979	419	18	para 1-4, medical indications	PGE_2	endocervical gel	0.1 mg	3.1	NR	4.0
		10				0.2 mg	7.4	NR	
		10				0.3 mg	NR	NR	
Wilson 1978	485	15	primigravidas, obstetric indications	PGE_2	extraamniotic	400 μg	4.5	33	7.3
		15		PGE_2	vaginal tablet	2 mg	2.5	20	10.2
		15		PGE_2	oral tablet	1 mg/hour × 10	1.6	0	12.7
		15		oxytocin	intravenous	initially 1 mU/minute, increasing as needed to maximum 128 mU/minute	1.1	0	13.8

NR = not reported

Oral Tablets

The 0.5 mg oral tablets have been tested for cervical priming but have proved less effective than extraamniotic treatment. The increase in cervical score — 1.6 to 4.2 points (464, 485) (see Table 3) — and the proportion of women going into labor before planned induction — 20 to 28 percent (350, 478) — were both less with oral tablets than with extraamniotic administration. One research group, administering 1 mg PGE_2 per hour orally for three doses, failed to find any significant improvement over placebos in the proportion beginning labor before induction or any reduction in the induction-to-delivery interval (161). The total dose of oral PGE_2 appears to influence results. Women taking 1 mg PGE_2 hourly for five hours achieved a mean increase in Bishop score of 2.0 points, excluding 44 percent who went into labor after priming (264). By contrast, another group, administered 1 mg per hour for 10 doses, recorded a mean increase of 4.2 points and a highly significant reduction in mean induction-to-delivery times compared with untreated controls and with women given 30 international units of oxytocin over 10 hours (464). In a study comparing extraamniotic, oral, and vaginal PGE_2 and intravenous oxytocin, the oral route was judged the least effective for prostaglandins on the basis of change in cervical score, percentage of women going into labor during priming and delivery intervals (485).

Vaginal Gels and Tablets

PGE_2 has been used vaginally for cervical priming, both in a viscous gel and in the standard tablet form. In one comparative study the vaginal route produced results midway between the extraamniotic and oral routes, when assessed on the basis of improvement in Bishop score, percentage of women in labor before induction, and delivery interval (485).

Ian Z. MacKenzie and Mostyn P. Embrey of the UK have done extensive work with PGE_2 vaginal gels for cervical priming in primiparas who required induction of labor for medical reasons. In these studies, which included women with both favorable and unfavorable Bishop scores, cervical priming produced shorter duration of labor, less need for epidural anesthesia, fewer cesarean sections, and higher Apgar scores than induction of labor without priming (310). MacKenzie and Embrey demonstrated that the number of women going into spontaneous labor during priming was proportional to PG dose and that the length of labor was inversely related to cervical score after priming, regardless of whether the women required subsequent labor induction (312). In these primigravidas, a single 5 mg dose of PGE_2 gel increased Bishop scores by a mean of 8.4 points and started labor in 69 percent. These double-blind studies also tested $PGF_{2\alpha}$: 25 mg of $PGF_{2\alpha}$ raised cervical scores by only 2.3 and brought on labor in only 13 percent (311).

Very low doses — 0.1 to 1.0 mg — of PGE_2 in a viscous gel have also been deposited endocervically (into the cervical canal) for cervical priming. Increases in cervical scores, extent of cervical dilation, and percentage of women going into labor all were dose-related. In an average of 2.6 hours after administration, all women receiving PG priming doses showed significant improvements in Bishop scores. For these parous women, labor lasted an average of 4 hours (419). PGE_2 by this route was clearly more effective than a placebo (487) or low dosages of oxytocin (455). The endocervical route may approach the vaginal route in effectiveness; more comparative studies are needed to settle this point.

In contrast to PG doses for labor induction, cervical priming doses are so low that uterine hypertonus is rare. If it occurs the fetus is usually not affected. Mean peak pressure during uterine

contractions initiated by the priming dose of PGE_2 has been recorded at 19 mm Hg, and pressure was never higher than 80 mm (419). The contraction frequency was 3.1 per 10 minutes, compared with 2.6 in controls given placebos (161).

Gastrointestinal side effects are infrequent, having been reported in only three studies. In two, fewer than one percent reported diarrhea and vomiting (312, 432); in the third, 21 percent experienced gastrointestinal side effects, including nausea (264). Shivering or transient fever was equally rare. Thus, for reasons of effectiveness, safety, and acceptability, PGE_2 is likely to be used increasingly for cervical ripening, either in conjunction with induction of labor or as an alternative procedure which may make induction unnecessary.

Extraamniotic administration appears to be the most effective route, based on studies so far, but vaginal tablets and endocervical gels have also produced good dilation with few side effects.

FIRST TRIMESTER ABORTION

When the first uses of prostaglandins to induce labor and to terminate pregnancy were reported in the late 1960s, some expected that these compounds could serve as a noninvasive, chemical method for early abortion (218). Subsequent research, however, while yielding new analogues, has not yet produced a first trimester PG method that is so easily managed that it can be widely used. For widespread use, a technique for first trimester termination should yield a very high rate of effectiveness, few incomplete abortions, a low incidence of minor side effects, no serious complications, and, preferably, should require only a single application that can be self-administered. To date vacuum aspiration meets most of these criteria better than prostagladins. With PGs, 5 to 15 percent of early terminations end in failure or incomplete abortion, requiring medical follow-up; uterine pain can be severe enough to require parenteral medication; and gastrointestinal side effects are a persistent problem. Furthermore, the absence of a proven luteolytic effect in women so far limits the usefulness of PGs in the first few weeks of pregnancy, when such a procedure would be especially useful because vacuum aspiration is less reliable then than it is after about the eighth week of pregnancy (136, 150). Nonetheless, PGs offer privacy and the potential for wide availability not possible with a clinic procedure. In the US and the UK, prostaglandins have not been licensed for first trimester use except on an investigational basis.

Nevertheless, research continues, especially into the development of vaginal suppositories containing PG analogues. These produce higher rates of effectiveness and completeness with fewer side effects than natural PGs or PGs administered by other routes. They are now being tested by the World Health Organization in Cuba, Egypt, Hong Kong, Hungary, India, Japan, Norway, Singapore, Sweden, Tanzania, the UK, the US, and Yugoslavia (489). New analogues are also being tested for intramuscular use. An alternative use of PGs in first trimester abortion, also being studied now, is dilation of the cervix before vacuum aspiration.

Among the prostaglandins, the natural PGs PGE_2 and $PGF_{2\alpha}$ are effective in the first trimester only by the intrauterine extraovular route and at doses so high that sedation for side effects is necessary. The analogues — especially 15-methyl-$PGF_{2\alpha}$ and 16,16-dimethyl-PGE_2 — are more effective than the natural PGs and more easily administered — intramuscularly and as suppositories — because they are longer acting. For example, the half-life of 15-methyl-$PGF_{2\alpha}$ in the circulation is 5 minutes; that of $PGF_{2\alpha}$ is 20 seconds (69). Because the analogues act more specifically on the uterus, they cause fewer side effects. Other analogues, not yet widely available commercially or still under study, may prove more effective with still fewer side effects. The new compounds include sulprostone (16-phenoxy-ω-tetranor-PGE_2 methylsulfonylamide), which has been tested extensively; ONO-802 (16,16-dimethyl-trans-Δ^2-PGE_1 methyl ester), now undergoing trials; and 9-deoxo-16,16-dimethyl-9-methylene-PGE_2, now in initial stages of clinical testing (see pp. 107-110).

Effectiveness

There are no large scale randomized studies specifically comparing the effectiveness of vacuum aspiration and PG abortion in the first trimester. Comparing individual clinical reports is difficult because of different definitions: some studies measure effectiveness in terms of the number of cases in which pregnancy did not continue, regardless of complications (150); other studies measure completeness, so that whenever a follow-up procedure is required — for example, to remove retained products of conception — the abortion is considered incomplete (57, 137). A recent US analysis of 65,000 procedures indicates that vacuum aspiration, the established practice for early pregnancy, is about 99 percent effective in interrupting pregnancy (150); rates of complete abortion, that is, the proportion of women not requiring further clinical procedures, range from 95 to 98 percent (57, 137).

With prostaglandins, two of the largest clinical studies to date showed that 15-methyl-$PGF_{2\alpha}$ methyl ester suppositories were effective in 91 or 100 percent of women, with complete abortion in 76 or 95 percent (173, 316) (see Table 4).

One small study in Sweden compared vacuum aspiration and PG suppositories of the unstable analogue 16,16-dimethyl-PGE_2 (303). In 78 women five to eight weeks after the last menstrual period, the rates of complete abortion were 93 percent for the PG and 95 percent for vacuum aspiration — not significantly different. Bleeding lasted an average of 11.9 days after the PG and 9.3 days after vacuum aspiration. As expected, the side effects of vomiting, diarrhea, and pain all occurred among the PG subjects only, but none took medication to prevent gastrointestinal reactions. All in the vacuum aspiration group were given sedation and paracervical anesthesia to control pain and possible vasovagal shock due to mechanical cervical dilatation, while 30 percent of the PG group took intramuscular analgesics for uterine cramps (303).

Vaginal Suppositories

The World Health Organization has sponsored international trials of vaginal suppositories containing 15-methyl-$PGF_{2\alpha}$ methyl ester. In studies of 1.0 and 1.5 mg suppositories of the $PGF_{2\alpha}$ derivative, repeated every three hours up to a total of four doses, four participating clinics reported effectiveness rates of 90 to 100 percent (69, 154, 156) (see Table 4). One center reported only 70 percent success with the 1.0 mg dose (156), and another, where women inserted the last three suppositories themselves, reported 65 percent and 70 percent effectiveness rates for the 1.0 and 1.5 mg doses, respectively (503). Subsequent, as yet unpublished studies may be able to improve on these initial results.

WHO trials have also tested suppositories of 16,16-dimethyl-PGE_2. With multiple doses, effectiveness rates have ranged from 82 to 100 percent (228, 312). The instability of the compound limits its practical application, however.

Table 4. First Trimester Abortion Induced by Prostaglandin Analogues, by Route of Administration and Analogue, Selected Recent Studies, 1976-1979

Author & Date	Ref. No.	No. of Women	Dosage	Gestation Length (in days LMP)	% Effective (% Complete)	% Experiencing Side Effects (Episodes per Woman) None	Vomiting	Diarrhea	Pain
Single vaginal suppository/15-methyl-$PGF_{2\alpha}$ methyl ester									
Dutt et al. 1979	134	17	3 mg	mean 45	94		94[a]		
Gréen et al. 1978	173	38	2 mg	≦ 49	100 (76)		37	32	
		35	2.5 mg	≦ 49	97 (86)		32	51	
		128	3 mg	≦ 49	100 (95)		54	59	
Kinra et al. 1978	243	58	3 mg	70-98	72		(0.8)	(1.4)	
Lauersen & Wilson 1979	274	18	3 mg	63-77	72				
MacKenzie et al. 1978	313	78	1 or 1.5 mg	mean 18	85	19	49	73	20
Mandelin 1978	316	104	3 mg	37-51	91 (76)	53	24	37(1.1)	66
Multiple vaginal suppositories/15-methyl-$PGF_{2\alpha}$ methyl ester									
Bygdeman et al. 1976	72	63	0.5-1.5 mg/3 hours × 3-4	31-49	100 (97)	42	—— 58 ——		
Fylling & Jerve 1977	154	30	1 or 1.5 mg/3 hours × up to 5	39-51	100		(3.0) (1.0)	(1.5) (2.5)	
Ganguli et al. 1978	156	20	1 mg/3 hours × up to 4	≦ 56	70		(0.2) (1.0)	(1.0) (1.1)	
Hamberger et al. 1978	186	42	1 or 1.5 mg/3 hours × 4	36-60	(93)				
MacKenzie et al. 1978	313	19	1 or 1.5 mg/3 hours	mean 22	95	21	63	53	53
Ylikorkala et al. 1976	500	40	1 or 1.5 mg/3 hours	41-55	98 (75)		40	65	
Zoremthangi et al. 1976	503	40	1 mg/3 hours 1.5 mg/3 hours	30-50	70 (68) 65		33	28	5
Multiple vaginal suppositories/16,16-dimethyl-PGE_2									
Karim & Ratnam 1977	228	12	750 μg/4 hours[b]	84-91	82		9	7	12
Lundström et al. 1977	303	50	.8, .8, 1, 1 mg at 3-hour intervals .8 mg × 4	35-56 35-56	NR (87) NR (94)		13	14	26 36
MacKenzie et al. 1978	313	14	1 mg/6-8 hours × 2	mean 20.2	100	69	8	31	31
		20	1 mg/3 hours × 4	mean 19.0	100	20	53	53	40
Intramuscular injection/15-methyl-$PGF_{2\alpha}$									
Fylling & Jerve 1977	154	24	600 μg single	30-60	92 (75)		(2)	(5)	
Seifert et al. 1978	395	19	250 μg/2 hours × 3-4	mean 45	90 (74)		32(1.8)[c]	32(1.8)	

NR = not reported

[a]Also, nausea: 65
[b]Researchers used the semicarbazone ester of 16,16-dimethyl-PGE_2.
[c]Also, nausea: 47(1.0)

Among single dose regimens of 15-methyl-$PGF_{2\alpha}$ methyl ester suppositories, a 3.0 mg dose has proved most effective. Success rates have ranged from near 70 to 100 percent (173, 243) (see Table 4). Plasma measurements show that in most women the concentrations of the analogue stayed at the therapeutic level of 1,200 pg/ml for three to six hours and remained above 900 pg/ml for 12 hours (173) (see Figure 3).

In suppository form, analogues of both PGE_2 and $PGF_{2\alpha}$ cause gastrointestinal side effects, but not as frequently as intramuscular and intravenous administration in other procedures. Side effects were lowest in a study by Karim using a single 750 μg dose of the p-benzaldehyde semicarbazone ester of the PGE_2 analogue; of 512 women studied, 9 percent experienced vomiting, 7 percent had diarrhea, and 4 percent had fever (228). PGE derivatives characteristically evoke fewer gastrointestinal side effects than $PGF_{2\alpha}$ derivatives, although aberrations in body temperature, such as chills, fever, and flushing, are more common (126). Unfortunately, PGE derivatives made up into suppositories are unstable unless they are kept deep frozen and used within a short time, a disadvantage for use outside of metropolitan facilities.

In a small study, a graduated, two-dose suppository regimen is showing better results than the single 3 mg suppository, with more even plasma PG levels. Niels Lauersen reported that,

after inserting a 1 mg 15-methyl-$PGF_{2\alpha}$ methyl ester suppository, and another 3 mg suppository three hours later, all 19 women aborted successfully, defined as a negative pregnancy test and no need for uterine evacuation. They were compared with 20 women given only a 3 mg suppository, of whom 75 percent aborted successfully. Those using the two-dose regimen had an earlier onset of uterine activity and slightly fewer side effects than did women starting with 3 mg (260).

Intramuscular Injections

Intramuscular injections of 15-methyl-$PGF_{2\alpha}$ (tromethamine salt) for first trimester abortion yield high effectiveness rates, similar to those obtained with suppositories, but side effects have been unacceptably high with the doses used to date. Unlike the native $PGF_{2\alpha}$, its 15-methyl analogue can be injected intramuscularly without causing local inflammation and pain (63). The rapid absorption and high PG levels in blood plasma that result, however, produce vomiting and diarrhea for about an hour after each dose (172). A trial using three to four 250 μg doses of 15-methyl-$PGF_{2\alpha}$ at two-hour intervals and another using a single dose of 600 μg both yielded effectiveness rates of about 90 percent and completion rates of about 75 percent, with bleeding starting about 3.5 hours after initial treatment (154, 395) (see Table 4).

Despite frequent side effects, intramuscular injections have three important advantages over vaginal application: (1) they can be used in much lower doses; (2) they are absorbed at a more consistent and predictable rate; and (3) injections are the most acceptable form of medication in many countries (358). Therefore, research is continuing with sulprostone and other new PG derivatives to improve this approach.

Mode of Action

PGs appear to induce abortion in the first trimester primarily through uterine contractions. These are probably stimulated both directly by the exogenous PGs and indirectly by enhanced release of endogenous PG (114, 174). Uterine activity recordings showed that the first response to a 3 mg suppository of 15-methyl-$PGF_{2\alpha}$ methyl ester was an increase in uterine muscle tone lasting about four hours, followed gradually by regular contractions (114, 262). In another study, ultrasonic scanning revealed that, about four hours after administration of a single 3 mg suppository, the conceptus was physically dislodged from the uterine wall; the rest of the uterine contents were expelled in three to nine days (134).

Plasma progesterone levels fall gradually after PG administration. The progesterone level registers a statistically significant decline in four to six hours (72, 114, 115), reaches 30 to 50 percent of the initial level in 24 hours, and by the end of one week falls to 10 percent of the initial level (see "Luteolysis," p. G-83). Although controversy remains, many researchers think that this decline is the result of uterine contractions, not the cause of them. The initial decline in progesterone presumably results from disruption of the developing placenta, which, along with the corpus luteum, secretes progesterone to maintain pregnancy. Alternatively, according to the "progesterone withdrawal" theory of Arpad I. Csapo, it is this decline in progesterone in the uterine smooth muscle that facilitates the development of regular uterine contractions after initial sustained (tetanic) contraction evoked by exogenous PG (114, 115). Some abortions take place without an appreciable drop in progesterone levels, however (72). This would seem to contradict the progesterone withdrawal theory, but the persistence of progesterone in the circulation makes it difficult to interpret the exact role of progesterone in regulating uterine contractions.

Clinical Events

With prostaglandins in early first trimester abortions, sometimes called menstrual regulation or MR (performed up to seven weeks after the last menstrual period), uterine cramping, although occasionally more severe, is usually similar to normal menstrual cramping (242, 500). Gastrointestinal side effects are common, however. While these side effects might be the major impediment to acceptance of PG suppositories for first trimester use, in one study Swedish women who used suppositories were more satisfied with the procedure than women who underwent vacuum aspiration procedures (372).

Uterine cramping or pain begins within 15 minutes to three hours. The onset is quick with intramuscular injection, slower with suppositories. In clinical trials about one-third of participants have asked for analgesic injections to ease pain (see Table 4). Women who have had dysmenorrhea do not appear to experience more severe pain than those who have not (303).

Bleeding begins in about 30 minutes to eight hours. The amount of blood loss is slightly greater than that lost in normal menstruation. One study reported a range of blood loss in the first 24 hours, measured by collection, from about 28 ml in nulliparas to 63 ml in women with two or more children and, subsequently, measured by standard extraction methods (184), 74 ml in both groups (186). Bleeding usually lasts 10 to 12 days, about 2 days longer than following vacuum aspiration abortions (304). Hemoglobin levels, measured within a week or two after the procedure, had fallen slightly in a few women, but not significantly (173, 303, 316). In the next menstrual period, blood loss is usually greater than normal. In one study 45 percent of women lost at least 60 ml, which was considered the upper limit for normal menstrual fluid volume (186).

Bleeding patterns in cases where the woman is not pregnant or where the abortion is incomplete may differ from those seen in cases of complete abortion. If the woman is not pregnant, she will bleed briefly or slightly for a few days, then have a normal menstrual period on schedule or a few days later (69, 242). Prolonged or excessive bleeding may indicate infection or incomplete abortion. Ultrasonic scanning has shown that small bits of conceptual tissue may remain in many women; this is without clinical import, however (134). Early in the first trimester evacuation of the uterus takes place over several days, and expulsion of conceptual tissue cannot be detected by an ordinary clinical exam.

The **gastrointestinal side effects** of PGs — nausea, vomiting, and diarrhea — may occur immediately and transiently after injections or more gradually and persistently with slow-release media; the timing of side effects is determined by PG levels in plasma (see Figure 4). Side effects are alleviated somewhat by premedication (296) and/or concurrent medication given either routinely or at the woman's request. Prochlorperazine (Compazine) is routinely used as an antiemetic, and a diphenoxylate and atropine combination tablet (Lomotil, Retardin), as an antidiarrheal. Analgesics have been administered either orally, rectally, or intramuscularly. In clinical trials, with treatment for side effects, about one-third experience vomiting; one-half, diarrhea (see Table 4).

Vaginal Devices

The analogue 15-methyl-$PGF_{2\alpha}$ methyl ester has been incorporated into slow-release vaginal devices made of Silastic 382, a

silicone rubber polymer, in an attempt to develop a mode of administration superior to suppositories. The devices were intended to reduce individual variations in absorption and to eliminate the multiple insertions required with suppositories. In addition, unlike suppositories, the devices remained intact at high ambient temperatures and could be retrieved if a woman reacted severely to PGs. These devices were used for second as well as first trimester abortion.

To date the vaginal devices have not lived up to expectations, however. Several researchers report that 20 to 60 percent of women expelled the devices, often unnoticed (192, 370). One clinic managed this problem by inserting a vaginal tampon or a diaphragm after the device (272). In some of the first devices, prostaglandin apparently crystallized on the surface of the device, causing erratic variations in drug absorption among individuals (410).

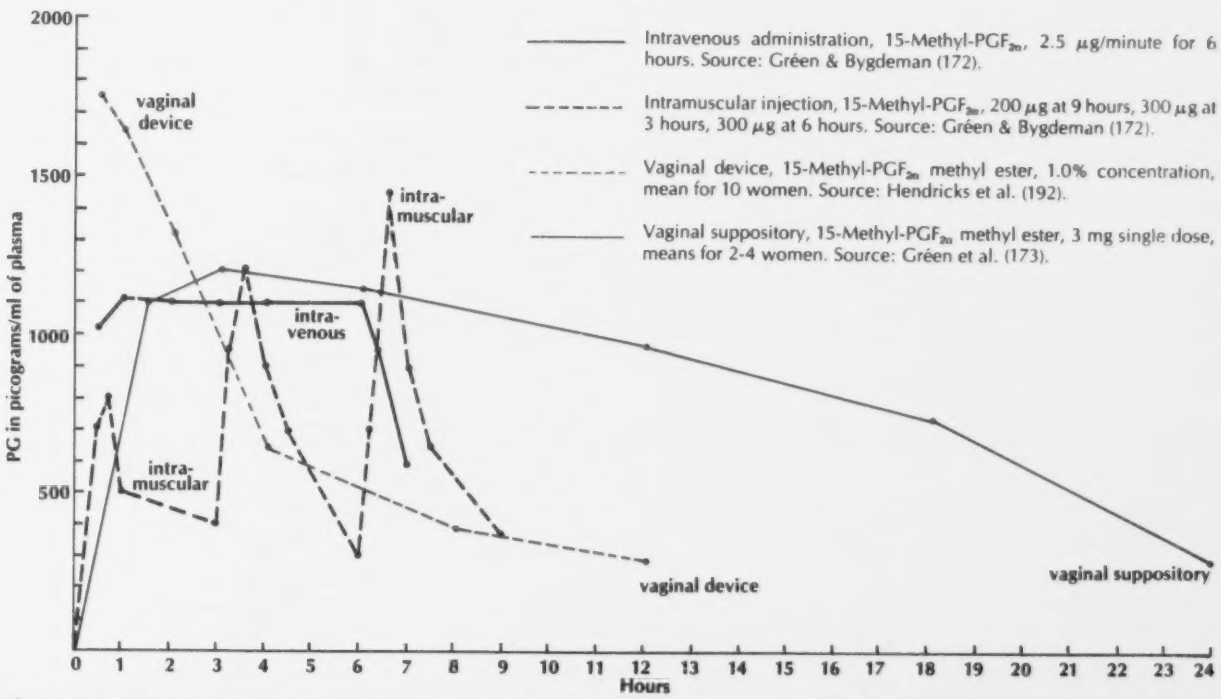
When the devices did stay in place and did release PGs at the appropriate rate, the more successful devices proved almost as effective as suppositories for both first and second trimester abortion. Drug absorption and therefore effectiveness appeared to depend on the concentration and the surface area of the device more than on the total drug content in the device (409). Overall success rates in the early first trimester ranged from 68 percent with a 0.2 percent concentration to 100 percent with a 0.5 percent concentration (see Table 5). In the second trimester, success rates ranged from 60 to 96.3 percent. The highest success rates have been achieved with the highest concentration studied — 1.0 percent (see Table 5). Even with the same devices, however, results have varied considerably (261).

Rates of vomiting and diarrhea have also varied, affecting anywhere from nearly all women in two small trials where they were not premedicated (192, 438) to less than half in trials with low-dose devices (see Table 5). In contrast with women given intramuscular injections, women with devices who were premedicated against vomiting and diarrhea could get along with concurrent medication only as needed instead of routinely (261). Occasional transient fever, flushing, or chills were reported (41, 69, 192, 370, 409, 438).

Cervical Dilatation

An alternative to using PGs to induce abortion in the first trimester is using them to dilate the cervix before vacuum aspiration. The intent of this "priming" of the cervix with PGs is to avoid pain and potential injuries from rapid mechanical dilatation. Women pretreated with PGs lose 30 to 50 percent less blood during vacuum aspiration than women not receiving PGs (155, 252, 266), and, according to initial studies, the incidence of cervical injury is considerably less (43, 96, 127). Where some mechanical dilatation is still needed, it can be accomplished easily because the cervix is softened by the PG (127). The drawbacks of using PGs for cervical priming before vacuum aspiration are that it may require an additional visit to the clinic or doctor's office and can cause gastrointestinal side effects.

Figure 4. Representative Blood Plasma Levels of 15-Methyl-$PGF_{2\alpha}$ and 15-Methyl-$PGF_{2\alpha}$ Methyl Ester Administered by Various Routes


2000
1500
1000
500
PG in picograms/ml of plasma
vaginal device
intra-muscular
intra-venous
intra-muscular
vaginal device
vaginal suppository
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Hours
Intravenous administration, 15-Methyl-$PGF_{2\alpha}$, 2.5 μg/minute for 6 hours. Source: Gréen & Bygdeman (172).
Intramuscular injection, 15-Methyl-$PGF_{2\alpha}$, 200 μg at 9 hours, 300 μg at 3 hours, 300 μg at 6 hours. Source: Gréen & Bygdeman (172).
Vaginal device, 15-Methyl-$PGF_{2\alpha}$ methyl ester, 1.0% concentration, mean for 10 women. Source: Hendricks et al. (192).
Vaginal suppository, 15-Methyl-$PGF_{2\alpha}$ methyl ester, 3 mg single dose, means for 2-4 women. Source: Gréen et al. (173).

The pattern of blood plasma levels of prostaglandins depends upon the mode of administration. It affects both abortifacient efficacy and rates of gastrointestinal side effects and pain. For example, with intramuscular injections, side effects are most common and most severe around the time that plasma levels peak, about one-half hour after injection.

Table 5. Abortion Induced by Vaginal Devices Containing 15-Methyl-$PGF_{2\alpha}$ Methyl Ester, Summary of Selected Studies, 1976-1978

Author, Date (Reference Numbers)	Characteristics of Device: PG Concentration (%)	Surface Area (in cm^2)	PG Content (in mg)	Total No. of Women	Gestation (in weeks)	% Effective
First Trimester						
Brenner et al. 1977 (41), Corson & Bolognese 1977 (103), Robins 1977 (370)	0.2	5	3	19	7	68
Brenner et al. 1977 (41), Bygdeman et al. 1976 (69), Corson & Bolognese 1977 (103), Robins 1977 (370), Thomas et al. 1978 (438)	0.5	10	5	43	9	89
Bygdeman et al. 1976 (69), Robins 1977 (370)	0.5	NR	10	24	9	100
Late First and Second Trimester						
Lauersen & Wilson 1976 (268)	0.25	20	5	10	8-14	60
Lauersen & Wilson 1977 (270)	0.5	10	5	20	12-20	54[b]
	0.5	10	5	28	12-20	95[b]
Lauersen & Wilson 1976 (268)	0.5	40	5	10	8-14	90
Bygdeman et al. 1976 (69)	0.5	NR	10	10	10-12	90
Dillon et al. 1976 (125), Lauersen & Wilson 1977 (267), Lauersen & Wilson 1976 (269), Lauersen & Wilson 1976 (272)	0.5	20	11	106	6-24	83
Bygdeman et al. 1976 (69), Dillon et al. 1976 (125), Hendricks et al. 1976 (192), Lauersen & Wilson 1976 (268)	1.0	20	11	54	8-20	96

NR = not reported

[a]Weighted averaged computed by dividing the total number of successful abortions in all studies listed by the total number of women involved in those studies.
[b]These two results were obtained with two shipments of devices in the same trial.

PG analogues, rather than natural PGs, have been the focus of research on cervical dilatation before vacuum aspiration. Various regimens have proved helpful. In one study, a single suppository of 2.0 mg of 15-methyl-$PGF_{2\alpha}$ methyl ester dilated the cervix to a mean 9 mm in six hours, while a 2.5 mg suppository in a slower-releasing base dilated the cervix to a mean 11 mm in 12 hours (155). In another study, a single suppository of 1 mg dilated the cervix to a mean 9.4 mm in 12 hours (266). (The cannulas commonly used in first trimester vacuum aspiration procedures are 6 to 12 mm in diameter, depending on the length of gestation.) In four separate trials, suppositories of 1.0 to 1.5 mg of 15-methyl-$PGF_{2\alpha}$ administered in four doses at three-hour intervals dilated the cervix at least 9 mm in all women (210) or at least 10 mm in 80 to 100 percent (95, 252, 504). Injection into the cervical tissue at two sites of 50 μg of 15-methyl-$PGF_{2\alpha}$ methyl ester has been studied but judged less effective than vaginal administration. Some 62.5 percent of cervices dilated to 10 mm or more within four hours (252).

With suppositories, gastrointestinal side effects and uterine cramping have ranged from what investigators termed "occasional" (155) or "tolerable" (266) to vomiting or diarrhea in 53 percent of women who were not premedicated (95).

The primary $PGF_{2\alpha}$, deposited in the endocervical canal in a viscous gel, has produced satisfactory dilation of the cervix. In one study, a 3 or 5 mg dose produced mean dilation of 12.5 mm after 8 to 12 hours (255). In another, a 3 mg dose dilated the cervix to a mean 14.3 mm in 10 to 12 hours (247). In this study, despite premedication, 70 percent reported pain and 36 percent vomited. The researchers who first used PGE_2 gel deposited endocervically before labor induction have now tested a very low dose of PGE_2 gel applied before evacuation at 10 to 12 weeks gestation. They used 0.5 mg PGE_2 to dilate 11 women from a mean of 5.4 to a mean of 10.7 mm in 12 hours. Cervical consistency scores increased significantly, an added advantage of PG priming over mechanical dilatation. The women felt no side effects except painful uterine contractions in 2 of 19 cases (523).

Newer PG derivatives produce the desired cervical dilation more quickly and with fewer side effects. Sulprostone has been

the subject of several studies on cervical priming (288, 376, 454, 476). Single 500 μg intramuscular doses yielded dilation of 10 mm or more for 72 percent of 93 women in four hours and for 97 percent in 12 hours (454). In two studies, injections of sulprostone into the cervical tissue resulted in dilation of 10 mm or more in almost all women (454, 476). In nonpregnant women undergoing hysteroscopy or other diagnostic procedures, however, sulprostone produced dilation of only 5 to 7 mm (300). A 500 μg vaginal suppository of 16,16-dimethyl-PGE_2-p-benzaldehyde-semicarbazone ester produced a mean 8 mm dilation in five hours. Women in this study, who took oral analgesics beforehand, reported no pain; of the 124 women studied, only one vomited and one suffered diarrhea (222).

In some women, PGs administered to dilate the cervix bring on abortion before the scheduled vacuum aspiration procedure. With 15-methyl-$PGF_{2\alpha}$ methyl ester suppositories, the proportion aborting before aspiration has ranged from 20 to 70 percent (95, 210, 266, 504); with $PGF_{2\alpha}$, the proportion was 29 percent in one study (247); with sulprostone, about 50 percent in two studies (288, 376).

Because of higher rates of incomplete abortion, gastrointestinal side effects, uterine pain, and somewhat more bleeding, prostaglandins currently available do not appear superior to vacuum aspiration for first trimester abortion. Yet vacuum aspiration, especially when it is not performed by skilled operators, also poses dangers — including traumatic mechanical dilatation of the cervix, reactions to anesthetic, perforation of the uterus, and (in rare cases) breaking the tip of the cannula. Also, the efficacy of vacuum abortion is somewhat lower before the eighth week of pregnancy than after (136, 150), whereas for PGs the reverse may be true (67) (see Table 4).

From a broader, less clinical perspective, PGs may eventually offer advantages in both cost and personal privacy over a method like vacuum aspiration, which requires surgical intervention. In the US, where abortion is legal and where facilities for vacuum aspiration are widely available, women seem to perfer a rapid, highly effective surgical procedure, whereas women in Europe and in developing areas might make greater use of a nonsurgical approach which can be used privately with relatively little hazard even though the process takes longer and involves greater discomfort. Since prostaglandins have now been proved relatively safe and effective for terminating early pregnancy, other factors — for example, the attitudes of women, the costs, the legal status, and the availability of various PG formulations and alternative procedures — may make more difference in determining the eventual use of these compounds than further clinical trials.

SECOND TRIMESTER ABORTION

Research on and use of PGs for second trimester abortion have grown substantially in recent years. $PGF_{2\alpha}$, either alone or in combination with other compounds, is now widely used as an intraamniotic agent in many developed countries. Large-scale collaborative studies show that $PGF_{2\alpha}$ induces abortion faster than hypertonic saline and, in most trials, more effectively, but, because of a larger number of incomplete abortions, it appears to have a higher complication rate. For early second trimester abortions — from the 12th through the 16th week — analyses by the US Center for Disease Control suggest that dilatation and evacuation (D&E) may be safer and more acceptable than either PGs or saline. Meanwhile, the $PGF_{2\alpha}$ analogue 15-methyl-$PGF_{2\alpha}$ was approved in 1979 in the US and India and is being tested internationally.

The advantages and disadvantages of PGs compared with other second trimester procedures are now being vigorously debated. The reasons are obvious. Second trimester abortion is legally and medically controversial. Between the 12th and the 24th week of pregnancy, the fetus develops rapidly in size. Fetuses aborted by instillation procedures late in the second trimester may in a few instances survive briefly outside the uterus. In the US, this has raised legal problems with respect to the responsibility of the physician and the institution for trying to maintain the life of the fetus (279, 369). From a medical standpoint, the health risks of abortion to the woman increase proportionately as pregnancy advances, although until the 24th week the health risks of abortion are less than those of live birth (88). From the 12th to 16th weeks, the 16th to 20th weeks, and after the 20th week, different techniques and instrumentation, each with particular benefits and risks, may be preferable both for the woman seeking abortion and for the abortion provider. To establish beyond doubt the safest and most acceptable procedure at each of these intervals will require controlled, randomized international trials, as well as continued observational and analytical comparisons (37, 82, 511).

Intraamniotic $PGF_{2\alpha}$

Since the US Food and Drug Administration (USFDA) in November 1973 approved its use, intraamniotic instillation of $PGF_{2\alpha}$ has been increasingly employed as a substitute for hypertonic saline instillation in second trimester abortions. It is now registered in 24 countries in Europe, West Africa, and the Americas, and also in Australia (10). In the US, in 1977 about 17 percent of reported second trimester abortions and 25 percent of those performed between 16 to 20 weeks were induced with intraamniotic $PGF_{2\alpha}$ (456). Debate about the relative safety of second trimester methods and concern about legal issues have slowed the shift to PGs, and some US centers reportedly have returned to the use of saline, which is toxic to the fetus, or have begun to use PGs in combination with other techniques such as urea (440).

The standard dose of intraamniotic $PGF_{2\alpha}$ is 40 or 50 mg, supplemented if necessary with an additional 10 to 40 mg 24 hours later or with another oxytocic (uterine stimulant) such as intravenous oxytocin or intramuscular 15-methyl $PGF_{2\alpha}$. With this regimen, studies show, abortion ensues in 88 percent (430) to 100 percent (279) of women, with complete abortion in 49 percent (430) to 84 percent (368). With $PGF_{2\alpha}$ the mean abortion interval is 20 to 25 hours (16, 430, 491), compared with about 30 to 35 hours with saline (17, 491). (See Table 6).

Relative Safety Debated

Some consider the rapid clinical acceptance of intraamniotic $PGF_{2\alpha}$ to be premature. Several recent, large-scale comparative trials in the US and elsewhere show that rates of major complications, most notably bleeding due to incomplete abortion, are higher with PGs than with saline (see Table 6). Two smaller, as yet unpublished studies show that complication rates with PGs also are higher than with D&E (178, 424). Because mortality is low with any form of legal abortion, differences in mortality among these methods are less valid statistically than differences in complications, which occur more often.

Because $PGF_{2\alpha}$ is a naturally metabolized, endogenous substance, it has been considered theoretically safer than saline,

which can adversely affect the circulatory system in various ways. Most major comparative studies belie this theoretical argument, however. Three of four have found that $PGF_{2\alpha}$ causes more complications than saline.

- A prospective study by the Joint Program for the Study of Abortion (JPSA), working with the US Center for Disease Control, comparing 1,241 $PGF_{2\alpha}$ abortions with 10,013 saline procedures performed between 1971 and 1975, found PGs associated with higher rates of endometritis, fever for one day or more, hemorrhage, convulsion, and surgery to manage complications. The risk ratio, or relative risk, of all serious complications (the ratio of those with complications to those without complications among the PG patients divided by the equivalent ratio among the saline patients) was 1.6 for $PGF_{2\alpha}$, or 60 percent higher. For the specific complications noted, the risk ratio for endometritis was 1.4; fever, 2.2; hemorrhage, 3.1; convulsion, 4.0; and surgical evacuation, 1.3 (181).
- In the World Health Organization Prostaglandin Task Force Collaborative Study, involving 717 women aborted by $PGF_{2\alpha}$ and 796 by saline (491), relative risks of PGs, as calculated by JPSA/CDC researchers, were frequently similar to those of the JPSA/CDC study: bleeding, 3.0; bleeding requiring transfusion, 4.1; and complications requiring surgery, 1.3 (84).
- The Indian Council on Medical Research Study on Sequelae of Induced Abortion found significantly more hemorrhage, immediate major and minor complications, infection, and late minor complications with PGs than with saline (430). Other Indian reports are mixed. One study found fever, convulsions, infection, and cervical trauma more common with PGs (159), and one reported significantly more gastrointestinal side effects and bleeding (28), but a third found more infection and hemorrhage requiring transfusion with saline (124).
- By contrast with these reports, comparative studies by the International Fertility Research Program compared 314 saline abortions, 274 abortions induced by repeated doses of $PGF_{2\alpha}$, and 328 induced by single doses of $PGF_{2\alpha}$ and found higher rates of hemorrhage requiring transfusion, more fever, and more infections associated with salines. PGs, however, produced higher rates of cervical injury, bronchospasm, and convulsions. Overall, excluding PG-related vomiting and diarrhea, saline produced more complications (42).

Table 6. Second Trimester Abortion Induced by Intraamniotic $PGF_{2\alpha}$ or by Hypertonic Saline, Selected Comparative Studies, 1973-1978

Author & Date	Ref. No.	Type of Study	Agent	Dosage	No. of Women	% Effective (% Complete)	Mean Hours Induction to Delivery	Significant[a] Differences in Side Effects, Complications, & Treatment for $PGF_{2\alpha}$
Berger & Edelman 1977	17	Retrospective	$PGF_{2\alpha}$	40 mg	100	100 (49)	25[b]	Less fever
			Saline	40 g	100	96 (61)	35[b]	
Bostofte et al. 1975	38	Prospective, nonrandomized	$PGF_{2\alpha}$	25 mg	25	92	37	NS
			Saline	≤ 40 g	25	72	46	
Corson et al. 1973	106	Retrospective	$PGF_{2\alpha}$	20 mg with serial increments	10	100 (60)	26	
			$PGF_{2\alpha}$	30 mg + 25 mg	10	70 (60)	25	
			$PGF_{2\alpha}$	30 mg with serial increments	40	98 (70)	21	
			$PGF_{2\alpha}$	40 mg + 40 mg	20	100 (55)	21	
			$PGF_{2\alpha}$	40 mg with serial increments	20	95 (70)	18	
			Saline	23-47 g	40	93	34	
Edelman et al. 1976	138	Multicenter, prospective, randomized	$PGF_{2\alpha}$	50 mg	128	93 (55)	20[b]	More gastrointestinal side effects, less fever
			$PGF_{2\alpha}$	25 mg with serial increments	114	98 (63)	17[b]	
			Saline	40 g	130	99 (73)	26[b]	
Grimes et al. 1977	181	Multicenter, prospective, nonrandomized	$PGF_{2\alpha}$	various	1,241	92 (56)	25	More fever, endometritis, hemorrhage, convulsions, antibiotic administration, major and minor operative treatments of complications, readmission to hospital
			Saline	usually 40 g	10,013	98 (60)	29	
Lauersen et al. 1974	276	Prospective, nonrandomized	$PGF_{2\alpha}$	20 mg with serial increments	10	90 (70)	15	
			Saline	40 g + oxytocin	10	100 (90)	20	

(continued on next page)

In a recent comparison of the efficacy and safety of intraamniotic $PGF_{2\alpha}$ and hypertonic saline for second trimester abortion, David Grimes and Willard Cates, Jr., of the CDC reviewed 15 different studies of these procedures and concluded that the superiority of $PGF_{2\alpha}$ over saline — the two most commonly used instillation agents in the United States today — has not been established (175).

There are several reasons for continuing questions over the relative safety of the two procedures:

(1) saline is an established procedure with which physicians have considerable experience, whereas prostaglandins were experimental for much of the period of which data are available; changes are still being made in PG formulations, dosages, and administration schedules.

(2) Although the more serious complications of saline have been rare in the reporting centers, when they do occur they are difficult to manage even in the best equipped facilities. They include hypernatremia (an excess of sodium in the blood); a decline in blood clotting factors (hypofibrinogenemia, or consumptive coagulopathy), which frequently occurs to a subclinical degree but on rare occasions can lead to hemorrhage, kidney failure, or death; and destruction of the uterine wall if the solution is injected there rather than intraamniotically.

(3) Because of these potential complications, saline is contraindicated for high risk women (for example, those with renal or heart disease), and the use of prostaglandins instead for these women could be expected to be accompanied by a higher incidence of complications.

(4) As experience is gained with specific complications of prostaglandin use, practitioners are finding ways to minimize them.

One reason, for example, that $PGF_{2\alpha}$ seems to produce higher complication rates is that it yields incomplete abortion more frequently than does saline. The consequences of incomplete abortion can be bleeding, infection, repeat hospitalization, and surgical evacuation of the uterus. Timely handling of delivery of the placenta may be able to reduce these complications. The Indian Collaborative Study has shown significantly more bleeding complications when the placenta is left in place for 30 minutes or longer (489).

Other specific PG complications can also be reduced or treated. For instance, transverse cervical laceration, thought to

Table 6. (Continued)

Author & Date	Ref. No.	Type of Study	Agent	Dosage	No. of Women	% Effective (% Complete)	Mean Hours Induction to Delivery	Significant[a] Differences in Side Effects, Complications, & Treatment for $PGF_{2\alpha}$
Nielsen et al. 1975	335	Prospective, randomized	$PGF_{2\alpha}$	40 mg + oxytocin	16	100	14	
			Saline	15-30 g + oxytocin	16	69	22	
Ragab & Edelman 1976	363	Prospective, randomized	$PGF_{2\alpha}$	50 mg	50	98 (42)	22[b]	More vomiting, diarrhea, pain (50 mg dose only); less nausea alone, chills/flushing
			$PGF_{2\alpha}$	25 mg with serial increments	50	98 (74)	20[b]	
			Saline	40 g	50	98 (57)	26[b]	
Risk et al. 1975	368	Retrospective	$PGF_{2\alpha}$	various	37	100 (84)		NS
			Saline	30-50 g	570	97 (88)		
Robins 1978	369	Retrospective	$PGF_{2\alpha}$	40 mg + oxytocin + laminaria	700	99 (73)	17	NS
			Saline	40 g + oxytocin + laminaria	170	99 (89)	18	
Stroup 1977	422	Prospective, nonrandomized	$PGF_{2\alpha}$	40 mg + laminaria	100	99 (65)	17	Less fever
			Saline	40 mg + laminaria + calcium gluconate	22	100 (64)	18	
			Saline	40 g	24	96 (54)	30	
			Saline	40 g + laminaria	37	100 (70)	21	
World Health Organization 1976	491	Multicenter, prospective, randomized	$PGF_{2\alpha}$	25 mg + 25 mg	717	86 (57)	20	More hemorrhage, blood transfusion, surgical reevacuation, dyspnea, flushing, chest pain[c]
			Saline	40 g	796	81 (55)	30	

NS = no significant difference

[a] $P \leq 0.05$
[b] Median time
[c] As calculated by Cates et al. (84)

Source: adapted from Grimes & Cates (175)

be more common in $PGF_{2\alpha}$ abortions than in saline abortions, is most likely in very young primigravid women whose PG abortions are augmented by oxytocin infusions (299). These injuries might be avoided by using laminaria or by omitting the oxytocin. Bleeding due to uterine atony (loss of muscle tone) probably can be prevented with intramuscular PG injections or continued oxytocin infusions (111, 238, 508). Transient fever without uterine tenderness, while not usually serious in itself, can create a clinical problem if it masks an actual infection and leads to misdiagnosis. Clinicians using PGs should remain alert to the possibility of infection with any fever even if the uterus is not tender.

Mortality statistics are as inconclusive as morbidity data (see Tables 7 and 8). In the US, the death-to-case rate for legal abortions using saline was about 16 per 100,000 procedures between 1972 and 1975; in 1976-1977, it fell to 3.5; the rate for prostaglandins and other agents has declined by about half in each two-year period for the last six years for which data are available — from 49.7 per 100,000 in 1972-1973 to 10.7 in 1976-1977 (82, 456). During the 16 to 20 week period, when more than three-quarters of 1972-1977 PG abortions were performed, the death-to-case ratio was 6.1 for instillation with PGs and other agents, 12.9 for D&E, and 19.3 for saline (456). Because the numbers are small — less than 50 second trimester deaths from all procedures between 1972 and 1977 — and the distribution of high-risk patients and early or late terminations may be shifting, these data are not conclusive. At least four of the six US women reported to have died following PG procedures before 1976 had serious preexisting conditions that contributed to their eventual deaths, and the deaths of the other two were at most tangentially related to PG administration (83). Since 1976, three or more deaths following PG procedures have been reported, two of otherwise healthy women due to cardiovascular collapse (87). The possibility that PGs may affect either the heart muscle or the circulatory system would warrant close attention if more such cases are reported (58, 87).

Indian studies have shown higher death rates associated with saline than PGs. In one case series, three of the five deaths among 507 saline patients were due to bleeding disorders or coagulopathy (124). Such disorders are apparently much more common in India than in the US, where they occur in only .3 percent of cases (175). Also, they are more serious in India because of the relative scarcity of sophisticated medical equipment (489). The other two deaths in this hospital series resulted from sepsis (124). In another series the four saline deaths among 1,152 cases were attributed to infection (123). The Indian Council of Medical Research reported one death in 507 women given saline and two in 1,295 given $PGF_{2\alpha}$ (430). In the Council's comparative study of $PGF_{2\alpha}$ and 15-methyl-$PGF_{2\alpha}$, three deaths occurred, one each in 430 given intraamniotic $PGF_{2\alpha}$, in 455 given intraamniotic 15-methyl-$PGF_{2\alpha}$, and in 1,569 given extraamniotic 15-methyl-$PGF_{2\alpha}$; all three deaths were due to hemorrhage (430). In summary, death-to-case rates in these series ranged from 197 to 986 per 100,000 for saline and from 122 to 154 per 100,000 for PGs.

While most of the early debate over relative safety focused on the two competing instillation procedures, PGs and saline, more recent data from the JPSA study suggest that D&E may be safer than either instillation method, at least between the 13th and the 16th weeks of pregnancy. Overall rates of hemorrhage and of retained products of conception were less than one percent with D&E, and only 9.9 deaths were reported per 100,000 cases (180). Moreover, the D&E procedure can be performed in less than an hour and causes no vomiting or diarrhea. It is usually done before 16 weeks gestation, when intraamniotic instillation is difficult. A comparison by Phillip Stubblefield of 406 D&E procedures up to the 16th week and 623 $PGF_{2\alpha}$ and laminaria procedures from 16 to 20 weeks produced no live fetuses and a significantly lower incidence of failed abortions, anemia, vomiting, diarrhea, pain, endometritis, and postdischarge bleeding with D&E than with PGs (424). In this study, as in the US aggregate data, the earlier gestation at which most D&E procedures are performed may help explain why its complication rate is lower, since complications increase in proportion to gestational age.

D&E, however, requires a skilled and experienced practitioner. Cervical injury is twice as frequent with D&E as with saline, and uterine perforation, six times as frequent (180). Also, local or general anesthesia, with its risks, is necessary. Further, dilating the cervix to as much as 14 mm, as required for D&E, somewhat increases subsequent risk of premature delivery (189, 490). This potential long-term complication may be mitigated by the use of laminaria or PGE_2 for cervical priming (523) as an adjunct to D&E, but this combined procedure will either require a second visit or a longer wait before the evacuation procedure.

Table 7. Deaths per 100,000 Legal Abortions, by Type of Procedure and Weeks of Gestation, United States, 1972-1977

Type of Procedure	Weeks of Gestation			
	13-15	16-20	21	Total
Prostaglandin or other instillation agents	32.6	6.1	40.5	10.8*
Saline instillation	2.5	19.3	20.6	15.5
D&E	6.7	12.9	16.7	8.3

Source: United States, Center for Disease Control (456).

Table 8. Deaths per 100,000 Legal Abortions, by Type of Procedure and Period, United States, 1972-1977

Type of Procedure	1972-1973	1974-1975	1976-1977	1972-1977 (95% confidence interval)
Prostaglandin	49.7	25.9	10.7	20.6* (9.4-37.5)
Saline instillation	16.9	16.0	3.5	15.5 (10.9-21.4)
D&E	4.8	8.6	10.2	8.3 (4.4-13.8)

Source: Cates et al. (86); US Center for Disease Control, in Benditt (15).

*The difference in the death-to-case rates for PGs and other instillations 1972-1977 in Tables 7 and 8 is caused by different estimates of the number of PG abortions performed, especially during 1972 and 1973 before PGs were licensed for US use. A total of 11 PG deaths occurred between 1972 and 1977 and this figure is the numerator for both rates. The denominator in Table 7 includes all abortions reported as "PG or other instillation agents" whereas the denominator used in Table 8 includes only procedures specifically identified as PGs.

Table 9. Second Trimester Abortion Induced by $PGF_{2\alpha}$ in Combination with Other Agents, Selected Studies, 1975-1978

Author & Date	Ref. No.	No. of Women	Inducing Agent(s) & Dosage	% Effective (% Complete)	Mean Hours Induction to Abortion (Nullip./Parous)	% Experiencing Side Effects	
						Vomiting	Diarrhea
Burkman et al. 1978	54	650	urea, 80 g + oxytocin, 32 mU/minute, intraamniotic	97 (59)	19.3	53	1
		1,083	above + $PGF_{2\alpha}$, 10 mg	98 (52)	15.1	73	5
Hodgson 1979	200	300	laminaria (1 to 11, mean 4.1, afternoon before) + $PGF_{2\alpha}$, 5 mg test dose staggered over 35 minutes, then 3.73 mg/hour by pump + oxytocin 167 mU/minute after 6-8 hours, continued for 2 hours after delivery	95 (93.7)	12.3	39	10
Kerenyi & Den 1979	239	508	amniocentesis of 50-400 ml + equal volume 20% saline replaced + $PGF_{2\alpha}$, 20 mg + oxytocin after contractions begin	99 (75)	16.1	33	0.8
Olund & Larsson 1978	340	23	Rivanol, 10 ml/week of gestation, 0.1% solution, extraamniotic	100	29.9	44	0
		23	above + $PGF_{2\alpha}$, 0.25 mg, then 0.75 mg/2 hours	100	24.9	39	0
Pahl & Lundy 1979	517	1,033	laminaria concurrently + $PGF_{2\alpha}$, 5 mg + saline, 50 ml, 20% solution + oxytocin after 24 hours	99 (67)	14.6	17	1.3
			above + laminaria the evening before		9.9		
Stubblefield et al. 1975	425	20	$PGF_{2\alpha}$, 40 mg, intraamniotic	67	29.4		
		243	above + laminaria for 14-18 hours	87	14.3		

For the woman seeking an abortion, a relatively quick procedure such as D&E under general anesthesia may be psychologically preferable to spending some 20 hours in discomfort and labor in order to expel a fetus vaginally. Nancy Kaltreider, Sadja Goldsmith, and Alan J. Margolis found that three weeks later women who had undergone prostaglandin abortions reported that they had experienced more pain than expected, were more depressed, had more guilt feelings, and were more likely to describe their experience as the loss of a baby than women undergoing D&E (216). The nurses also found the instillation procedure stressful. On the other hand, from the physician's point of view, D&E requires instrumentation of the pregnant uterus and fetal dismemberment and thus can also be disturbing (216).

These issues and others relating to second trimester abortion in the US were discussed at a 1979 conference in Chapel Hill, North Carolina (15, 82). Marc Bygdeman of the Karolinska Institute in Sweden was more optimistic about the prospects for PGs than US researchers. He subsequently pointed out that in the US, where outpatient clinics perform most early abortion procedures, D&E might be more suitable, but in Sweden and other countries where surgery is less frequent and most abortions are performed in hospitals, the preferred method might be different (15).

PGs With Other Techniques

The consensus of the Chapel Hill conference and the conclusion to be drawn from recent clinical research is that prostaglandins used in conjunction with other methods may be more effective and more acceptable than currently available PGs used alone (15, 424). T.D. Kerenyi, for example, one of the pioneers in the use of saline, has shifted from saline to a combination of urea and prostaglandins (238). PGs are now increasingly used with intraamniotic urea or extraamniotic Rivanol to hasten the evacuation process. At the same time, laminaria are also applied when appropriate to help dilate the cervix. (See Table 9.)

Urea is an alternative to saline as a hyperosmolar solution for midtrimester abortion by intraamniotic instillation. It was approved for this purpose by the USFDA in 1979. Urea is as effective as saline, and, like saline, toxic to the fetus, but, unlike saline, it is not toxic to the woman if misinjected. Mean abortion intervals are longer, ranging from 43.7 hours (364) to 51 hours (8) with urea alone or, combined with high doses of oxytocin, 18 hours (56) to 43.4 hours (477). The chief advantage of urea over saline is that theoretically the risk of serious complications is less because urea readily crosses cell membranes and so is easily eliminated from the body (250).

Low doses of PG added to the usual 80 mg dose of urea markedly shorten abortion intervals. The fetus may be expelled as early as 10.5 hours after instillation when 10 mg PGE_2 is the augmenting agent (109). $PGF_{2\alpha}$, however, is more convenient because it is more stable. Doses of $PGF_{2\alpha}$ from 2.5 mg to 20 mg have been tested, but PG dose has little effect on abortion interval. With high-dose oxytocin (332 mU/minute) given intravenously, Theodore King and Ronald Burkman at The Johns Hopkins University have reported mean abortion times ranging from 15.1 to 18.3 hours (54, 241). The shortest mean abortion intervals with urea plus $PGF_{2\alpha}$ were obtained with a 10 mg dose plus oxytocin: 15.1 hours (54) and 13.1 hours (479). With

this low PG dose, there were few side effects, particularly little transverse cervical laceration and diarrhea (54). The dose was subsequently reduced to 5 mg (53). In two Indian studies comparing $PGF_{2\alpha}$ plus urea, 40 mg $PGF_{2\alpha}$ alone, and saline plus oxytocin, mean abortion time was shortest with $PGF_{2\alpha}$ plus urea in one (327) but with saline plus oxytocin in the other (290). In both studies, $PGF_{2\alpha}$ plus urea produced the lowest complication rates.

Rivanol (ethacridine lactate, or 6,9-diamino-2-oxyethyl acridine lactate) has been used extraamniotically for second trimester abortion in Japan for 20 years (314). There are said to be no contraindications or specific complications (254), although gastrointestinal side effects occur in about 30 percent of women (340). The method, which entails instilling 10 ml of a 0.1 percent solution for each gestational week, up to 150 ml maximum, takes an average of 28 to 30 hours to effect abortion, even with intravenous oxytocin as an augmenting agent (254, 340).

Pilot studies suggest that combining PGs with Rivanol may improve its effectiveness. Repeated, low extraamniotic doses of $PGF_{2\alpha}$ with Rivanol reduced mean abortion intervals by four to five hours in one study, but gastrointestinal side effects increased from about 30 to 50 percent (340). Augmenting Rivanol with two intramuscular injections of 15-methyl-$PGF_{2\alpha}$ cut mean abortion intervals down from 29.5 to 21.3 hours and boosted success rates from 78 to 88 percent, but the side effects were just as common as with systemic PGs alone (251, 366).

There is some evidence that Rivanol, like saline and urea, works by causing endogenous PG release. Indomethacin, an inhibitor of PG synthesis, prolongs Rivanol abortions (338); Rivanol increases lysozyme and free arachidonic acid content in amniotic fluid — both are indicators of PG activation (339, 341). More work with Rivanol, now in progress under the supervision of the WHO, may reveal another way to induce abortion with lower doses of PGs (489).

Laminaria are the dried and sterilized stems of the sea plant *Laminaria digitata*. Inserted into the cervical canal, they absorb moisture, swell, and slowly dilate the cervix (183). When laminaria are put in place several hours before PG administration, most conveniently the evening before, their use reduces abortion intervals by six to eight hours (26, 485) or more (425). Leaving the laminaria in place for only four hours proved slightly less effective (420). Inserting laminaria the evening before urea and PG instillation further shortens abortion intervals for this combined technique — a mean of 8.7 hours in one study, counting from the time of intraamniotic injection (485). In other studies, where oxytocin also was used, inserting laminaria at the time of instillation did not hasten fetal expulsion (420, 479).

ONO Pharmaceutical Company, Japan, markets oral tablets of PGE_2 in Japan, Korea, and Taiwan. (ONO)

15-Methyl-$PGF_{2\alpha}$ Analogue

The $PGF_{2\alpha}$ analogue 15-methyl-$PGF_{2\alpha}$, longer acting than the natural compound, is also being tested for use in second trimester abortion by a variety of routes of administration — intraamniotic, extraamniotic, intramuscular (in the tromethamine (tham) salt), and, in its methyl ester form, vaginal (see Table 10). Applied by the intraamniotic and vaginal routes, the analogue shows results comparable to those of $PGF_{2\alpha}$. Extraamniotic administration permits abortions between 13 and 16 weeks gestation but has a lower completion rate than other routes. Intramuscular injections produce severe gastrointestinal side effects. The analogue has been approved in 1979 in India for intramuscular, intraamniotic, and vaginal use between the 6th and 16th weeks (410) and in the US for intramuscular use in the second trimester.

Intraamniotic administration. Administered intraamniotically, a single injection of 2.5 mg of 15-methyl-$PGF_{2\alpha}$ (tham salt) is at least as effective as a 50 mg dose of $PGF_{2\alpha}$. Success rates are about 88 to 98 percent. In fact, in four comparative trials of 2.5 mg of 15-methyl-$PGF_{2\alpha}$ and 40 or 50 mg of $PGF_{2\alpha}$, the analogue proved more effective than the natural prostaglandin (397, 430, 494, 499). Abortions were complete in 46 to 77 percent of cases (19, 397, 430, 494, 499) — a range comparable to that for the parent compound. Mean abortion times — about 18 to 20 hours — were slightly shorter than with $PGF_{2\alpha}$ (19, 397, 430, 494, 499). Uterine pain and gastrointestinal side effects came on more gradually with the analogue than with $PGF_{2\alpha}$ (499), but gastrointestinal side effects as well as other, rare side effects such as shivering, dyspnea (breathing difficulties), and flushing were slightly more common, perhaps indicating sustained high plasma levels of PG. Acute bleeding was less common in one study (499). On balance, except for the possibility of using a single 2.5 mg injection, the analogue administered intraamniotically displays no distinct advantage over the native $PGF_{2\alpha}$.

Vaginal suppositories. In the form of suppositories, 15-methyl-$PGF_{2\alpha}$ methyl ester induces abortion more quickly than by intraamniotic instillation. Side effects are only slightly less frequent than with intramuscular injections, perhaps because plasma levels of PG remain at prolonged high levels, rather than form abrupt peaks. (Plasma levels after various modes of administration are shown in Figure 4, p. G-93.)

WHO tested 15-methyl-$PGF_{2\alpha}$ methyl ester suppositories in 310 women at seven locations worldwide. With repeated doses of 1.5 mg of triglyceride suppositories, 91 percent aborted within 30 hours. The mean interval was 13.1 hours for parous women and 15.3 hours for nulliparas. The women took antidiarrheal medication, but still 70 percent reported loose stools — an average of 2.8 episodes each among those affected — and 67 percent vomited — again 2.8 times each, on the average (495). The slightly less potent unesterified 15-methyl-$PGF_{2\alpha}$ (tham salt) has yielded similar effectiveness rates — 80 to 97 percent, but a longer mean abortion interval — 19 hours (27, 330, 468).

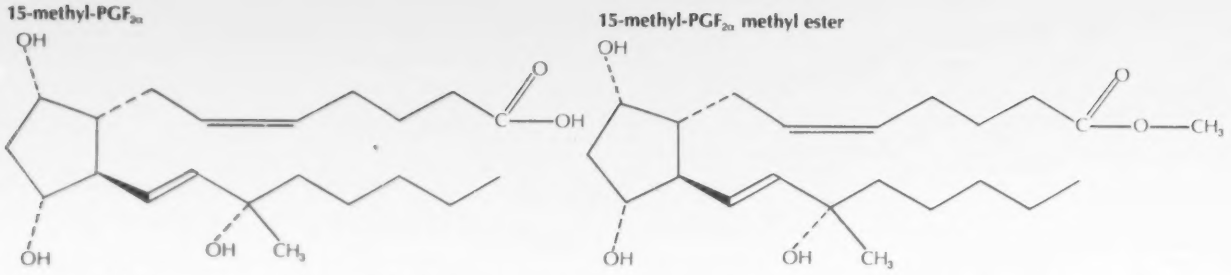


Figure 5. Both 15-methyl-$PGF_{2\alpha}$ and 15-methyl-$PGF_{2\alpha}$ methyl ester, analogues of the native $PGF_{2\alpha}$, have been tested extensively for induction of first and second trimester abortion and have been suggested for treatment of intrauterine death and to stop postpartum bleeding.

A single 3.0 mg suppository proved slightly less effective than repeated suppositories. The Indian Council on Medical Research, studying 288 women, reported abortion in 79 percent after 30 hours and 58 percent complete abortions. Vomiting and diarrhea occurred in three-fourths of the women, but other complications were few (431). In a Swedish study, 79 percent of 62 women aborted in an average of 13.3 hours, and all abortions were complete in 36 hours after an intramuscular injection of 15-methyl-$PGF_{2\alpha}$ (68); a trial in Finland achieved 78 percent effectiveness in 24 hours with a mean interval of 17.9 hours (317). By contrast, in a New Delhi study the suppositories were only 48 percent effective in 30 hours with a mean abortion interval of 15.4 hours in parous women and 20.7 hours in nulliparas (206).

With the 3.0 mg suppository, PG levels in plasma were detectable after two hours and averaged 200 to 400 pg/ml over 4 to 12 hours. By 24 hours they were undetectable. Cramps and side effects persisted as long as PG levels were measurable. Individual PG readings varied considerably, possibly because of inconsistent release by the suppositories or individual variation in vaginal absorption. The clinic investigating plasma levels found that all of the failed abortions in their studies involved suppositories from the same lot (11). Research to develop better suppository media to improve the performance of intravaginally administered PGs is continuing.

Vaginal devices containing 15-methyl-$PGF_{2\alpha}$ methyl ester also have been used for second trimester abortion. Success rates are similar to those of suppositories (see "Vaginal Devices," pp. G-92–93).

Extraamniotic administration. The advent of the long-acting 15-methyl derivative of $PGF_{2\alpha}$ makes it possible to induce abortion with a single extraamniotic dose of 1 mg or less. Several trials, including the WHO study of 660 women at 10 centers, showed that abortion intervals are relatively brief, averaging 13 to 17 hours (199, 254, 430, 493). Side effect rates are also relatively low, with vomiting and diarrhea reported in about one-third of the women. Effectiveness rates are disappointing, however. Only 77 to 90 percent of these women aborted

Table 10. Second Trimester Abortion Induced by 15-Methyl-$PGF_{2\alpha}$ or 15-Methyl-$PGF_{2\alpha}$ Methyl Ester, by Route of Administration, Selected Recent Studies, 1977-1979

Author & Date	Ref. No.	No. of Women	Dosage	% Effective (% Complete)[a]	Mean Hours Induction to Abortion (Nullip./Parous)	% Experiencing Side Effects	
						Vomiting	Diarrhea
Intraamniotic/15-methyl-$PGF_{2\alpha}$							
Tejuja et al. 1978	430	430	2.5 mg	88 (49)	20.6/17.7	42	24
World Health Organization 1977	494	919	2.5 mg	95 (52)	18-20	[b]	[b]
Extraamniotic/15-methyl-$PGF_{2\alpha}$							
Tejuja et al. 1978	430	1,569	1 mg	78 (23)	15.4/13.6	37	34
World Health Organization 1977	493	660	0.92 mg	80 (32)	16.2/13.1	38	32
Intramuscular injection/15-methyl-$PGF_{2\alpha}$							
Lange & Secher 1977	259	80	250 μg/2 hours	98	18.2/16.4	79	86
World Health Organization 1977	492	515	250 μg, then 300 μg/3 hours	85 (35)	15.7/13.7	[c]	[c]
Vaginal suppositories/15-methyl-$PGF_{2\alpha}$ methyl ester							
Tejuja et al. 1979	431	288	3 mg	79 (58)	14.7	72	77
World Health Organization 1977	495	310	1.5 mg/3 hours	92 (50)	15.3/13.1	67	70

[a]Effectiveness and completion rates differ among studies in part due to differing time limits and/or criteria.
[b]Episodes per woman: vomiting: 2.5; diarrhea: 1.1.
[c]Episodes per woman: vomiting: 2.9; diarrhea: 2.8.

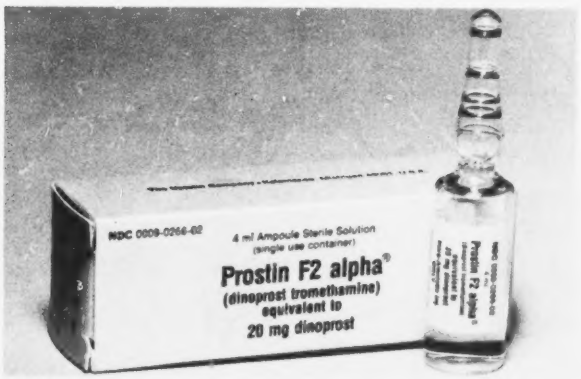
within 36 hours, perhaps because the uterine activity caused by the single PG dose began to subside too soon. The completion rate of 32 percent was the lowest of all the routes of administration examined by the WHO PG Task Force.

Intramuscular injection. The analogue 15-methyl-$PGF_{2\alpha}$, unlike the naturally occurring $PGF_{2\alpha}$, can be injected intramuscularly without causing severe pain or local inflammation. By this route, the $PGF_{2\alpha}$ analogue has induced midtrimester abortion in 85 percent or more women within 30 hours after they received 200 μg initially, then 300 μg repeated every three hours (492); in 90 percent or more given 250 μg every two hours (193, 259, 407); and in 95 percent given an individualized accelerated dose regimen (275). Because of systemic distribution and abrupt spikes in plasma PG levels, even with prophylactic medication, women averaged 5 to 11 episodes of vomiting and diarrhea in most studies (19, 158, 259, 407, 492) — so frequent that most investigators ruled out injections for routine use. In a review of 815 abortions by various dosages, most often 250 μg every two hours, 68 percent of the women vomited and 61 percent had diarrhea (392). One researcher remarked that his patients grew anxious anticipating the injections and subsequent side effects (193). Uterine pain seemed to be less with 15-methyl-$PGF_{2\alpha}$ than with $PGF_{2\alpha}$ (407, 492), and uterine bleeding was less because, unlike single-dose methods, intramuscular PG administration can be continued after membranes rupture to contract the uterus and decrease local blood flow (19).

Intramuscular injections can be useful to complete an abortion that failed after another type of procedure. Thus PGs can be an alternative to repeat intraamniotic injection, oxytocin infusion, or surgery. In one trial, the intramuscular approach proved effective in 92 percent of cases, producing complete abortions in an average of 5.3 hours and incomplete abortions in 11.9 hours (105). In another it proved effective in 100 percent within 3.8 or 5.8 hours in parous women and primiparas, respectively (271).

The 15-methyl derivative of PGE_2 in methyl ester form has also been tested intramuscularly and proved effective. It causes fever and chills more than gastrointestinal side effects (29, 265). Like most PGEs, this analogue is so unstable that it must be stored frozen and then refrigerated up to the time of use.

Although prostaglandins have proved faster than saline in effecting abortion, the long period of contractions, the high incidence of diarrhea and vomiting, the complications of incomplete abortion, bleeding, and fever, and the possibility of producing a live fetus have militated against wider use in the US. Between the 13th and 16th weeks, D&E, when performed by skilled practitioners, appears to be safe, more effective, and more acceptable to US women than prostaglandins. After the 16th week or under different conditions it is not yet possible to determine conclusively what the best procedure is. Research is underway, both with prostaglandins used in combination with other procedures such as instillation of urea and with new PG analogues, to minimize side effects and complications.



$PGF_{2\alpha}$ is marketed worldwide by the Upjohn Company under the brand name Prostin F2 alpha.

OTHER OBSTETRIC USES

In addition to inducing labor at term and abortions in the first and second trimester, PGs are used to induce labor in some cases of intrauterine fetal death and similar problems and to control postpartum bleeding. Intrauterine death in pregnancies of less than 18 or 20 weeks gestation is also called missed abortion and, in more advanced pregnancies, fetal death. Fetal death in utero before onset of labor occurred in about one percent of consecutive deliveries in two series (129, 447). PGs are also recommended for anencephaly (393) and as primary oxytocic agents in cases of hydatidiform mole (502).

Where death has occurred in utero, about 90 percent of the time labor will ensue naturally within three weeks (129, 447). Nevertheless, it is prudent to empty the uterus within a few weeks after death is diagnosed because of the psychological trauma for the woman as well as the risk of coagulation disorders which increase after the fetus has been retained for five weeks. After an intrauterine death, the blood clotting protein fibrinogen may gradually fall, increasing the risk of hemorrhage. In a series of 33 cases of fetal death, fibrinogen had declined linearly for several weeks in 30 percent and was below normal when first measured in 35 percent. Three women developed severe hemorrhage (360).

Prostaglandins can be both effective and safe in bringing on labor in cases of intrauterine death. Oxytocin even when infused for 12 to 24 hours is not always effective (42, 166, 289, 298, 463). Saline is more hazardous in these cases than PGs because the woman's tissue absorbs the solution more readily with a dead fetus in utero and because the risk of blood coagulation disorders is greater (42, 415). PGE_2 is more effective in managing cases of fetal death than in terminating intact second trimester pregnancies.

In a multicenter trial with 20 mg PGE_2 suppositories, 97 percent of 709 women with confirmed diagnosis of missed abortion or fetal death were delivered successfully in a mean 10.7 hours (411). The 11 women who were not delivered with PGE_2 alone (1.9 percent) had sufficient cervical dilation to allow uterine evacuation by other means. Operator experience was not a factor in the results. The side effects in these women, who were medicated only occasionally, were: vomiting, 56.4 percent; diarrhea, 42.7 percent; and transient fever, 40.2 percent. There were no cervical injuries. In addition to the short induction intervals and high success rates, vaginal suppositories for fetal death yield a high rate of complete as contrasted with incomplete abortion — 87 percent in the collaborative study. Thus, most patients do not require a surgical procedure.

Several small studies have explored other routes for administering PGs. One combined intramuscular 15-methyl-$PGF_{2\alpha}$ and laminaria to deliver six women with missed abortion (399). The laminaria were inserted the evening before, and antiemetics and antidiarrheal drugs were taken 2 and 10 hours before PG injections began. These women aborted in 4 to 24 hours, or

an average of 9 hours, after two to four 250 mg injections. Medication limited gastrointestinal side effects to one to three episodes per woman (399). Another study, involving 11 cases of fetal death and 2 of anencephaly, reported an average induction interval of 7 hours, using intramuscular injections of 15-methyl-$PGF_{2\alpha}$ only (501). A lower dose of $PGF_{2\alpha}$, combined with urea and administered intraamniotically, induced labor in 20 women with an intrauterine death usually persisting two to three weeks and produced very few side effects (403). These women had 100 ml of amniotic fluid removed and replaced with 70 mg of urea in saline, 30 mg of $PGF_{2\alpha}$, and antibiotics. They averaged 13.2 hours until delivery, and among them suffered three incidents of nausea, two transient fevers, and two hemorrhages, one of which was due to a fibrinogen defect. In cases of prolonged fetal retention, however, intraamniotic instillation may be technically difficult, because much of the amniotic fluid has been resorbed, and risky because the placental membranes permit rapid absorption of PGs or hypertonic solutions.

PGs have also been used successfully in cases of hydatidiform mole (a benign cystic tumor derived from conceptual tissue) and anencephaly (a congenital defect where much of the brain is absent). Over 50 cases of molar pregnancy terminated with prostaglandins by various routes were reported in the literature up to 1975 (514). A further 27 cases were treated with 20 mg PGE_2 suppositories repeated at two to five-hour intervals. Eighty-five percent of these women were delivered in a mean 11.5 hours. They were all subsequently evacuated with suction and/or curettage. Side effects included vomiting in 63 percent, diarrhea in 30 percent, and fever in 22 percent. Bleeding over 500 ml occurred in 48 percent. One woman was found to have carcinoma and was treated with hysterectomy and chemotherapy (520). These studies found PGs the most convenient and effective means of evacuating molar pregnancies, although uterine curettage is necessary to insure complete removal of all potentially carcinogenic tissue.

Although the number of women with mole and anencephaly treated with various PG modalities is too small to permit conclusions, several practical points on management have emerged:

- So-called "PGE_2 reactions" — a combination of rapid breathing and heart rates, high fever, hypotension, vomiting, and diarrhea — have indicated that the 20 mg PGE_2 suppository may be too large a dose for some women, particularly in the third trimester (326, 353, 390). In fact, the PGE_2 suppository has not been authorized in the US for use in fetal death or hydatidiform mole past 28 weeks gestation (459). One possible solution has been to use a portion of a suppository, adjusting the dose to the individual (390).
- Blood coagulation monitoring is important in cases of intrauterine death so that low fibrinogen levels may be treated if necessary, even though this complication has been observed only rarely in recent studies (375, 403).
- If PG induction fails, one possible reason, even in the third trimester, is that the pregnancy is extrauterine (153, 346).

Postpartum Bleeding

Although there are few published articles on the subject, many US clinicians seem to be using 15-methyl-$PGF_{2\alpha}$ (tham salt) in the form of intramuscular injections to treat postpartum or postabortion bleeding due to uterine atony (111, 238, 508). Because postpartum hemorrhage is a common and potentially serious complication of delivery, oxytocic drugs are routinely given after delivery, thereby minimizing the risk of severe bleeding.

The ONO Pharmaceutical Company distributes $PGF_{2\alpha}$ under the brand names Prostarmon-F and Prostaglan. (ONO)

Oxytocics such as PG injections also can prevent or reverse postabortion syndrome, a condition due to uterine atony. The syndrome can be characterized by severe pain, shock symptoms, and an enlarged uterus sometimes without severe bleeding (263, 380), and it can occur anywhere from immediately to several days after a uterine evacuation. As treatment, uterine aspiration is required along with the oxytocic (423).

The first use of $PGF_{2\alpha}$ to control bleeding was reported by Shigeo Takagi in Japan (521). He used $PGF_{2\alpha}$ intravenously and intramuscularly, at first with poor results. He then shifted to multiple injections directly into the myometrium, either transvaginally or transabdominally, with good results. He found $PGF_{2\alpha}$ equally effective in primiparas and multiparas, regardless of how much blood was lost before PG therapy began (521). The $PGF_{2\alpha}$ did not affect blood coagulation factors or injure the myometrium.

Because the 15-methyl-$PGF_{2\alpha}$ analogue is more specific and, injected intramuscularly, more convenient to use, it may be even more suitable for this use than natural $PGF_{2\alpha}$. Further clinical testing is warranted.

PG INHIBITORS

Primary dysmenorrhea is painful menstruation associated with ovulatory cycles. It typically begins soon after onset of menstrual cycles in young women and generally subsides after the first pregnancy. These women experience intermittent cramps and dull ache in the pelvic region; most may also suffer from nausea, vomiting, diarrhea, palpitations, dizziness, flushing, sweating, or headache — the same symptoms seen in women given exogenous PGs. Estimates of the incidence of dysmenorrhea range all the way from 3 to 90 percent of women (328, 482, 498), depending on whether one considers as diagnostic criteria a visit to an emergency room, absence from work or school, confinement to bed, use of analgesics, or simply loss of efficiency due to pain (20). Dysmenorrhea used to be considered one of the unavoidable burdens of being a woman, to be endured stoically, or taken as evidence that females were prone to psychosomatic illness. Now specific, effective drugs, PG synthesis inhibitors, are available to relieve much of the pain and other symptoms.

The chief cause of primary dysmenorrhea is now thought to be the prostaglandins that emanate from the endometrium shortly before and during menstruation. Three lines of argument implicate PGs in this process:

(1) dysmenorrheic symptoms are identical to side effects in women receiving high doses of PGs for abortion;
(2) PGF levels in the endometrium increase from proliferative through secretory to menstrual phase during ovulatory cycles and are higher than normal in the endometrium, endometrial jet washings, and menstrual fluid of dysmenorrheic women; and
(3) specific PG synthesis inhibitors reduce these high PG levels, normalize uterine activity, and relieve dysmenorrheic pain.

The exact process by which excessive PGs accumulate in the endometrium, reach the myometrium, and cause dysmenorrheic pain is unknown. PG levels may be abnormal because of greater synthetic enzyme activity (498), because of excess release of PG precursor acids (194), or because of a deficiency in PG metabolizing enzymes (257). Perhaps uterine pain receptors are sensitized to PGs or their biologically active endoperoxide precursors (498) or metabolites (305). Dysmenorrheic women are not more responsive than other women to intrauterine administration of PGs, however (301). Although the peripheral symptoms of dysmenorrhea resemble PG side effects, Vivecca Lundström has calculated that the plasma PGF metabolite levels are not high enough to produce the observed effects. Perhaps PGs released locally — for example, in the gastrointestinal tract — may be causing such symptoms as diarrhea (305).

Dysmenorrheic cramps arise both from uterine hyperactivity and from uterine ischemia, or deficient blood supply. Heightened uterine contractions, recorded as pressures of 200 to 300 mm Hg, are well documented in dysmenorrhea, compared with peak pressures of around 100 mm Hg in normal menstruation. The threshold for dysmenorrheic pain is considered to be 150 mm Hg. The basal tone, or resting pressure between contractions, is also usually above the normal level of

Table 11. Treatment of Primary Dysmenorrhea with Prostaglandin Synthesis Inhibitors, Selected Double-Blind Studies, 1974-1979

Author & Date	Ref. No.	Study Type	No. of Women	Dosage	Start of Treatment (Relative to first day of menses)	Assessment Criteria	% Experiencing Relief	Side Effects
ARYLACETIC ACIDS								
Alclofenac								
Boullaye et al. 1971	39	placebo crossover	48	500 mg 3 ×/day	Day 1	drug preference vs. placebo	56	1 fatigue 1 nausea
ARYL PROPIONIC ACIDS								
Anaprox								
Henzl & Izu 1979	194	placebo	227			pain relief, supplementary medication, daily activity	78	1%, nausea 1%, light-headed
Henzl et al. 1979	196	crossover	24	1,100 mg, single dose	*	pain intensity difference, uterine pressure	100	1 nausea
Ibuprofen								
Dingfelder & Staurovsky 1977	128	placebo crossover	48	400 mg/4 hours	Day 1	pain relief score, drug preference vs. aspirin or placebo, daily activity, supplementary medication, relief of associated symptoms	significantly better than aspirin or placebo	6%, acid stomach, nasal congestion, drowsiness
Layes Molla & Donald 1974	277	crossover	67	400 mg × 2	Day −1	drug preference vs. placebo, degree and duration of pain relief	64	6%
Ketoprofen								
Kauppila et al. 1979	235	crossover	23	500 mg 4×/day	Day −1	dysmenorrhea score, duration of associated symptoms, work absenteeism, blood loss	88	50%, gastrointestinal
Naproxen								
Dandenell et al. 1979	119	placebo crossover	97	250 mg up to 5/day	Day 1	pain, number of tablets, daily activity, menstrual flow	71	like placebo, but more flatulence
Kajanoja & Vesanto 1979	215	crossover	24	250 mg as needed	Day 1	pain, menstrual flow, number of capsules	61 moderate to good	21%, gastrointestinal
FENAMATES (anthranilic acids)								
Flufenamic acid								
Anderson et al. 1978	4	crossover	30	200 mg/8 hours	Day 1	dysmenorrhea symptoms, drug preference, number of capsules, number of supplementary medications, absenteeism	77	

*2-hour study of immediate relief

about 0 to 10 mm Hg. Moreover, contractions often occur at more frequent intervals in dysmenorrheic women. Probably the dull ache of menstrual pain is due to low blood supply in the uterus, since these pressures are well above systolic blood pressure and compress uterine blood vessels (498).

Newer analytical methods for measuring PGs in the myometrium throughout the menstrual cycle and in menstrual fluids have established even more definitively than did older techniques that PG levels are higher in dysmenorrheic women than in those who are not dysmenorrheic or in those who have been treated with PG inhibitors. Vernon R. Pickles and colleagues were the first to demonstrate elevated PG levels in dysmenorrheic subjects. They originally isolated a human "menstrual stimulant" and later showed that this was a mixture of PGE and PGF. In their classic study, bioassays of 4,950 menstrual "specimens" and endometrial curettings showed an excess of PGF over PGE in cases of dysmenorrhea (356).

In normal menstrual cycles, endometrial PGE content increases two- to threefold from proliferative to menstrual phase, and PGF content increases three- to fourfold (130, 405). Analysis by radioimmunoassay has shown that PGE and PGF concentration in dysmenorrheic endometria were three times higher at late secretory phase than in normal tissue (484), and determinations by gas-liquid chromatography-mass spectrometry have shown mean $PGF_{2\alpha}$ concentrations four times higher than normal in dysmenorrheic endometria on the first day of menstruation (305). Similarly, in women with dysmenorrhea the quantity of PGF released per cycle was twice as high as normal when bioassayed from tampon extracts (92), three times as high in concentration when radioimmunoassayed from cervical cup specimens (394), and five times as high per cycle when radioimmunoassayed in tampon extracts (502).

Over 40 clinical trials have demonstrated excellent results in treating primary dysmenorrhea with PG synthetase inhibitors. Trials record relief of dysmenorrhea in 60 to 100 percent of cases, as assessed by various criteria. (Table 7 lists controlled trials of these drugs, organized by class of drug.) Several studies have recorded uterine activity before and during drug treat-

Table 11. (Continued)

Author & Date	Ref. No.	Study Type	No. of Women	Dosage	Start of Treatment (Relative to first day of menses)	Assessment Criteria	% Experiencing Relief	Side Effects
Kapadia & Elder 1978	217	placebo crossover	44	200 mg 3×/day	Day 1	pain relief, vomiting and diarrhea, menstrual flow	82 significant pain relief	9%, dizziness or mild dyspepsia
Mefenamic acid								
Anderson et al. 1978	4	crossover	30	500 mg/8 hours	Day 1	drug preference vs. flufenamic acid, dextropropoxyphene-paracetaool combination, absenteeism, number of tablet and supplementary medications, dysmenorrhea symptoms	93	1 dizziness & nausea 1 headache 1 deep venous thrombosis
Budoff 1979	51	placebo crossover	34	250 mg 4×/day	Day 1	symptom frequency and severity, supplementary medication	significant difference from placebo	9%, gastrointestinal 3%, sleepiness
Tolfenamic acid								
Kauppila & Ylikorkala 1977	236	placebo crossover	27	133 mg 3×/day	Day −2	pelvic and back pain, absenteeism, menstrual flow, nausea, vomiting, diarrhea, all compared with indomethacin and placebo	88	"no marked side effects"
INDOLES								
Indomethacin								
Hamann & Laursen 1977	185	placebo crossover	60	100 mg + 25 mg 3×/day	Day 1	drug preference vs. placebo, daily activity, blood loss, supplementary medication, associated GI symptoms	90	23%
Kajanoja & Vesanto 1979	215	crossover	24	25 mg, 2-6 capsules/day as needed	Day 1	pain, menstrual flow, number of capsules, results compared with naproxen	73 moderate to good	29%, gastrointestinal 25%, central nervous system
Kauppila & Ylikorkala 1977	236	placebo crossover	27	25 mg 3×/day	Day −2	pelvic and back pain, absenteeism, menstrual flow, nausea, vomiting, diarrhea	87	"no marked side effects noted"
PYRAZOLES								
Phenylbutazone								
Black 1958	31	open	24	100 mg 3×/day	Day −2	complete or marked relief of dysmenorrheic pain and associated symptoms, daily activities	88	
SALICYLATES								
Acetylsalicylic acid (aspirin)								
Janbu et al. 1979	208	placebo crossover	30	500 mg 4×/day	Day 1	pain, blood loss, drug preference vs. paracetamol, placebo	no significant difference among drugs	3%, cardialgia

ment. They document marked reduction in contraction amplitude, frequency, and especially tone (116, 301, 302, 361, 362) (see Figure 5). Also, women report less menstrual blood loss (5, 51, 119, 236). Treatment with the PG synthetase inhibitors indomethacin, ibuprofen, and naproxen reduced high PGF levels in menstrual fluid to below normal (92, 362, 394). Indomethacin also lowered the concentration of circulating plasma PGF metabolite, which has some PG-like activity, to undetectable levels (305). Thus PG levels, which normally rise from the proliferative to the secretory phase and rise even higher in the menstrual phase, become abnormally high in dysmenorrhea, but they return to normal after treatment with PG inhibitors.

The newer PG synthetase inhibitors — naproxen, flufenamic acid, ibuprofen, mefenamic acid, and tolfenamic acid — help 75 to 95 percent of women. Often they eliminate dysmenorrheic symptoms such as diarrhea and vomiting even when uterine discomfort is not entirely alleviated. By contrast, some older, less potent PG synthesis inhibitors recently re-evaluated — aspirin, acetominophen, and dextropropoxyphene — showed no significant effect on symptoms (207). The practice, common with older PG inhibitors, of starting medication up to three days before the expected menstrual flow is not necessary with the newer compounds (301), thus avoiding any danger of drug exposure during a potential pregnancy.

In general, the side effects of PG synthesis inhibitors at high doses include gastrointestinal upsets like those seen with aspirin and, rarely, central nervous system effects such as headaches, mood changes, and dizziness. Other, even less frequent side effects include drug rash, blood disorders, bronchospasm, and liver and kidney disorders. The side effects of PG synthesis inhibitors at high doses in chronic users are well studied, since these drugs — also known as nonsteroidal anti-inflammatory agents — were originally approved in the US for relief of rheumatoid arthritis and gout. With the new PG inhibitors, side effects are seen in 10 percent of women or fewer and are limited usually to headache, dizziness, and gastric disturbances. The older PG synthesis inhibitor, indomethacin, tends to cause more side effects, especially when taken at higher doses; for example, 56 percent of women taking 50 mg three times daily suffered from side effects (35). Further, indomethacin and butazolidine are more likely to cause side effects other than gastric discomfort.

The mode of action of PG inhibitors in alleviating dysmenorrhea has been reasonably well documented. These drugs act by inhibiting the first enzyme in PG synthesis, cyclooxygenase (481). There is evidence that some inhibitors — for instance, the fenamates (a group of anthranilic acid derivatives) — also block PG action at the target tissue, stopping contraction of the human myometrium, for example (381).

PG inhibitors are now also being tested with promising results in the treatment of other gynecological conditions involving excessive endometrial PG levels, pain, bleeding, or uterine activity such as premature labor, dysmenorrhea due to IUD insertion (59, 321) or an IUD in situ (18, 446), endometriosis (31, 49, 234), and postpartum uterine pain (34). Many investigators have observed that dysmenorrhea decreases under placebo treatment, but the PG synthesis inhibitors are markedly more effective. They are more specific than oral contraceptives and progestins and, unlike steroids, need not be used throughout the cycle to be effective. They are definitely superior to other palliatives which have been recommended from time to time such as heating pads, vitamins, diet, alcohol, rest, exercise, hypnosis, psychotherapy, cervical dilatation, curettage, presacral neurectomy, hysterectomy, or pregnancy.

Premature Labor

PG synthesis inhibitors also can be used to quiet uterine activity in cases of premature labor, thus permitting gestation to continue. Research is in the early stages, however, and potential side effects on the fetus are unknown. The PG inhibitors used to date include indomethacin and flufenamic acid.

In a placebo-controlled test of indomethacin (25 mg every four hours for 24 hours), labor was arrested and did not recommence within 24 hours in 12 of 15 (80 percent) compared with 5 of 15 (33 percent) of controls, a result that did not quite achieve statistical significance (33). In a series of 50 women 31 to 32 weeks pregnant who received 100 mg of indomethacin in a rectal suppository, then 25 mg orally every six hours until 24

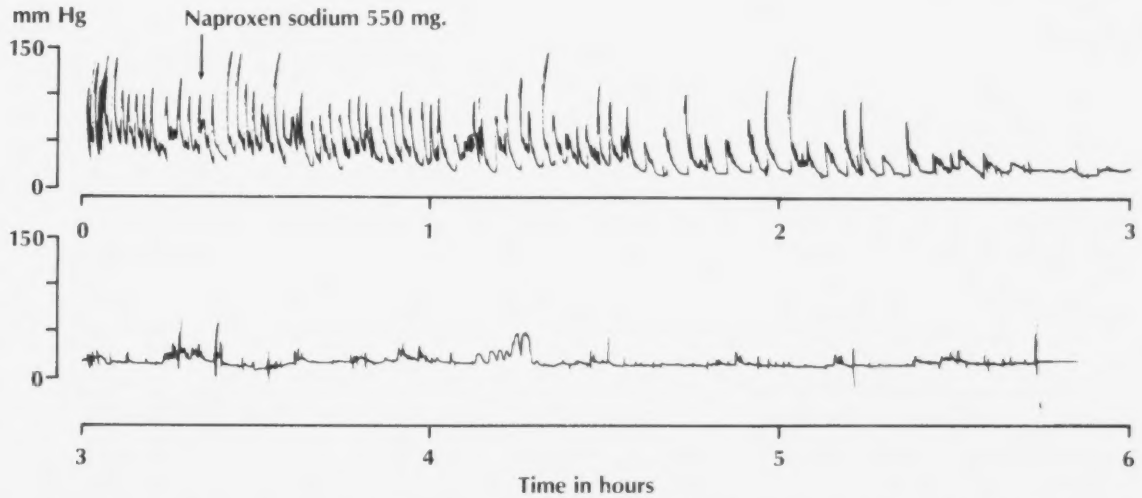


Figure 6. Recordings of uterine pressure show how a 500 mg dose of naproxen sodium quiets dysmenorrheic uterine contractions. Within two hours contractions have diminished and pain has disappeared.

Source: Lundstrom and Green (305)

hours after contractions ceased, 38 mature infants were delivered. This series was extended to 300 cases without any adverse effects observed in the infants born at term (505). Another clinic prescribed the same oral dose of indomethacin and succeeded in postponing delivery in eight of nine women in premature labor at 29 weeks or more (488).

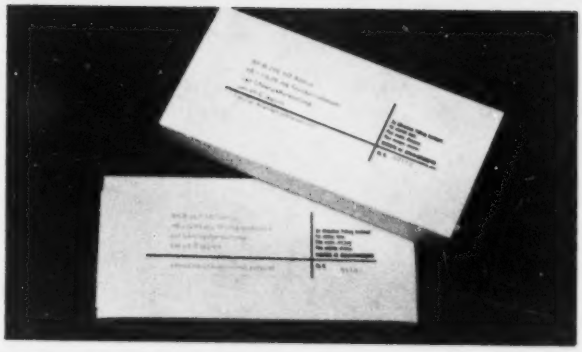
In another study, the fenamate drug, flufenamic acid, controlled premature labor for 48 hours or more, arrested uterine activity, and normalized PGF metabolite levels in 15 of 18 women (87 percent). These women, 28-36 weeks pregnant, took 200-400 mg flufenamicacid every 1-2 hours initially, then every 6 hours for four days. They experienced no gastrointestinal or respiratory side effects. There were 11 mature and 4 premature infants born an average of 17.9 days later. Two had symptoms suggesting possible pulmonary hypertension or distress, but both improved; one fetus was stillborn due to placental separation (519).

Previously, the only way to control preterm labor was to administer a less specific agent such as alcohol or a β-adrenergic drug. Because PG inhibitors interfere with all PG synthesis, they may compromise the circulation of the fetus by prematurely closing the ductus arteriosus. One of the functions of endogenous PGs in utero is to maintain this opening between the pulmonary artery and the aorta, to shunt blood past the fetal lungs. A few such incidents of closing the ductus have been reported during treatment with indomethacin (315) and aspirin (9) for other purposes. Minimal doses of PG synthesis inhibitors are used to stop premature labor, and none of the studies has reported serious problems.

NEW DERIVATIVES

Much of current prostaglandin research aims at developing better PG analogues — PGs with prolonged action, more specific effects on target tissues, greater stability, and fewer side effects. The analogues most thoroughly investigated — 15-methyl-$PGF_{2\alpha}$ and its methyl ester — clearly improve upon natural PGE_2 and $PGF_{2\alpha}$. They are as effective as the natural PGs or more so; often lower doses administered at longer intervals produce the same desired effects. The 15-methyl or 16,16-dimethyl groups joined to synthetic PGs hamper the action of 15-PG-dehydrogenase, the first enzyme that inactivates the PG; as a result, the PG is longer acting. Furthermore, some side effects — for example, pain at the site of an intramuscular injection — have been attenuated with the currently available analogues. Others, however — such as gastrointestinal and body temperature effects — remain difficult to manage. The stability of the compounds also remains a problem. The instability of the natural PGE_2 at room temperature is well known, but instability also characterizes some of the otherwise much improved derivatives of PGE_2.

How to solve all the problems of PGs in one synthetic compound is the puzzle facing PG researchers. Results have often been frustrating, as in the case of 16,16-dimethyl-PGE_2-p-benzaldehyde semicarbazone ester. For abortion, the analogue has proved effective, with few side effects. Over 90 percent of 54 women in the late first trimester and the second trimester aborted within 36 hours after receiving up to four vaginal suppositories containing 750 μg each. Although prophylactic medication was limited to intramuscular analgesics with no antiemetics or antidiarrheal agents given, only five women vomited, three had diarrhea, and two had transient fever — a



Sulprostone (SH B 286), manufactured by Schering AG, may soon be registered in West Germany. (Schering AG)

marked improvement over results with PGE_2 (228). For cervical dilation, again the new drug proved effective and caused few side effects. Cervices of 70 percent of 124 women in the first trimester were dilated to 8 mm or more within five hours after administration of a single suppository. There was only one instance of diarrhea and two of transient fever (229). Yet this effective and well-tolerated drug can be kept only two weeks in suppository form, deep frozen at -4° F, because of the instability of the natural PGE_2 ring. The search for new PG derivatives is beginning to yield analogues that improve upon older PGs in one or several ways. Among the new derivatives now being studied are three with primarily oxytocic effects, one with enhanced stability, and two with potentially luteolytic effects.

Sulprostone

Sulprostone is a PGE_2 derivative with remarkably selective oxytocic effects. Developed by Pfizer Incorporated, USA, its formula is 16-ohenoxy-ω-tetranor-PGE_2 methylsulfonylamide (see Figure 7). It was tested clinically between 1974 and 1978 in over 5,000 women from 13 countries under the auspices of Schering AG of Berlin (454).

Initial animal studies showed that sulprostone aborts guinea pigs 43 to 44 days pregnant solely by stimulating uterine contractions; it is not luteolytic in rats (142, 197). Sulprostone did not stimulate the guinea pig small intestine or cause bronchoconstriction in histamine-primed guinea pigs, as do other PGs (142), suggesting that it would be associated with little diarrhea or asthma.

Clinical trials at first concentrated on intravenous administration because it permits good control over dose rates, blood levels, and, consequently, side effects. Later trials have explored the extra- and intraamniotic routes and, more recently, the intramuscular route. Vaginal suppositories have proved relatively ineffective (388). In these clinical trials, as a rule women received no premedication for nausea, vomiting, or diarrhea, as is virtually universal practice with natural PGs and their other analogues. With sulprostone, diarrhea is very rare; nausea with or without vomiting is somewhat more common. Since sulprostone very specifically stimulates the uterine myometrium, pain or cramps are a characteristic complaint, and during clinical trials women frequently have been given pain medication. A feature of most of these clinical studies is the inclusion of first and second trimester abortions and sometimes mole and missed abortion or fetal death all in the same series of cases.

Administered intravenously in trials involving primarily abortion patients, sulprostone proved moderately successful. Side

Table 12. Abortion and Labor Induced by Sulprostone, by Route of Administration, Selected Studies, 1977-1980

Author & Date	Ref. No.	No. of Women	Description of Cases	Dosage	% Effective (% Complete)	Mean Hours	% Experiencing Side Effects: Pain	Nausea	Vomiting	Diarrhea	Other
Intravenous											
Schüssler et al. 1979	390	14	abortion, 5-12 weeks	1.7 μg/minute for 5 hours to maximum 500 μg	29 (7)	12.2	29	36	21	0	
		77		1.7 μg/minute for 10 hours to maximum 1,000 μg	87 (77)		26	13	8	1.3	cold & fever: 2.6
		40		2.8 μg/minute for 6 hours to maximum 1,000 μg	65 (55)		48	38	30	0	cold & fever: 2.5
		35		4.1 μg/minute for 6 hours to maximum 1,500 μg	66 (29)		83	68	54	3	cold & fever: 14.3
Ulbrich & Bartels 1978	454	298	1st & 2nd trimester abortion; missed abortion; mole	250 μg/hour to maximum 1,500 μg	72						all: 51
		121		250 μg/hour to maximum 1,000 μg	64						all: 55
Extraovular											
Dennemark & Semrau 1978	122	111	1st trimester abortion	25 μg	96		49	— 28 —			other: 6
Karim et al. 1977	226	240	abortion, 5-6 weeks	50 μg	95		14		5	0	headache: 4
Ulbrich & Bartels 1978	454	599	1st & 2nd trimester abortion, missed abortion; mole	25 or 50 μg	73						all: 29
Intraamniotic											
Lichtenegger 1977	287	15	abortion, 13-29 weeks	828 μg	90	17.2					headache: 11
Van den Berg & Niermeijer 1978	466	4	abortion, 20 weeks or more, all young nulliparas	1 mg	50	26	0	— 0 —		0	
		20		2 mg	55	20	35	— 30 —		10	
		22		3 mg	68	14	9	— 5 —		0	cold: 6; drowsiness: 6
		18		4 mg	96	17	83	— 22 —		6	shock: 6
Intramuscular injection											
Csapo et al. 1980	112	90	mean 7 weeks	2 × .5 mg/4 hours in 81%	96 (96)		66		26	10	endometritis: 2
Karim et al.1978	223	20	abortion, 14-24 weeks	0.5 mg/4 hours	90	18.0		15	20	5	cold: 0
		20		1 mg/8 hours	90	20.5		10	40	10	cold: 5
		20		1 mg/6 hours	95	18.25		15	30	10	cold: 5
Lehmann 1978	280	49	abortion, 13-31 weeks; fetal death; anencephaly	0.5 mg/4 hours to mean 5.9 injections	98 (61)	18.3	51	51	41	6	
Schmidt-Gollwitzer et al. 1978	389	21	1st & 2nd trimester abortion (93% and 7%, respectively)	0.5 mg	57 (48)						
		29		0.5 mg/4 hours × 2	72 (55)						
		25		0.5 mg/6 hours × 2	80 (52)		32	18	13		
		44		0.5 mg/8 hours × 2	77 (55)						
		61		0.5 mg/4 hours × 3	82 (51)						
Ulbrich & Bartels 1978	454	138	1st & 2nd trimester abortion; missed abortion; mole	0.5 mg/4 hours	95						all: 51
		26		0.5 mg/6 hours	96						all: 23
		153		1.0 mg/6 hours	93						all: 41

effect rates were low compared with rates for intravenous administration of other PGs; irritation at the infusion site was negligible. Doses ranged from 1 to 2 mg over 3 to 10 hours. A dose rate of 1.7 μg per minute over 10 hours, totaling 1 mg, was the most effective, with the fewest side effects (391). Success rates in most studies have ranged from 70 to 100 percent; mean abortion times have varied from 8 to 12 hours; pain has occurred in 40 to 80 percent of women, and other side effects in 20 to 30 percent (384).

The extraamniotic route, as expected, elicited fewer peripheral side effects and allowed lower doses: 25 to 50 μg proved effective. Several clinicians have reported success rates of 70 to 100 percent, with mean abortion times of 12 to 18 hours. Uterine pain occurs in about half of the women; other complaints, in 20 to 30 percent (384).

Intraamniotic instillation of sulprostone also has been effective, with fewer side effects than with the older analogues. Doses of 1 to 4 mg administered via the vagina produced abortion in 50 to 96 percent of nulliparas. Uterine pain was dose-related and occurred in up to 15 percent of the women, but other side effects appeared not dose-related (466). In another series, 16 of 18 women given .823 mg sulprostone aborted successfully in a mean 17.2 hours, with two headaches the only reported side effects (287).

Intramuscular injection of sulprostone is currently under study in some clinics in Europe. Most report success rates of 93 to 100 percent, usually after two or three 500 μg doses at 4- to 6-hour intervals. Nausea or vomiting rates usually hover around 30 percent, and uterine pain, around 30 to 50 percent (384). Many researchers have commented on the absence of side effects in the majority of women, the lack of cervical trauma, and the general acceptance of this method by women (384). In fact, several consider sulprostone the preferred method for midtrimester abortion (182, 389, 465).

Arpad Csapo and colleagues have reported good preliminary results in the US, Finland, and Hungary in terminating early first trimester pregnancies (menstrual induction) (112). One to four injections four hours apart in 90 women an average of 45 days after their last menstrual period produced complete abortion in 96 percent. Side effects included cramps requiring sedation in 66 percent, vomiting in 26 percent, and diarrhea in 10 percent. In interviews with about half the women, 90 percent were satisfied with the procedure and of those who had previously experienced surgical interruption, 89 percent preferred the pharmacological method (112). More research of this nature, testing which procedures women prefer, would be useful, once efficacy and safety have been established.

Given by the intracervical or intramuscular route, sulprostone can dilate the cervix in late first trimester. In three studies, 25 μg injected into cervical tissue (intramurally) dilated 98 percent of women sufficiently for vacuum aspiration in 4 hours (454) or 83 and 90 percent in 12 hours (40, 454). Karim was able to aspirate 75 percent of his abortion patients without further cervical dilatation three hours after they received 500 μg intramuscularly, and the remainder were dilated to 4 to 7 mm at that point (225). Side effects occurred in 15 percent or fewer in all these studies.

Since sulprostone administered by the noninvasive, intramuscular route is effective and acceptable even without premedication against vomiting and diarrhea, it clearly improves upon natural $PGF_{2\alpha}$. Further, it does not elicit fever or chills like natural PGE_2. For early first trimester use, it may eventually become an acceptable alternative to vacuum aspiration. Schering AG is currently completing a license application to the German Federal Health Authority for sulprostone (387).

ONO-802

Another uterine-specific PG analogue, 16,16-dimethy-trans-Δ^2-PGE_1 methyl ester — ONO-802 — has progressed to clinical trials (see Figure 7). It is 10 to 100 times as potent as the primary PGs — PGE_1, PGE_2, and $PGF_{2\alpha}$ — measured by its contractile effect on the pregnant rat uterus. While the parent compound PGE_1, has a less potent effect on the uterus than PGE_2 or $PGF_{2\alpha}$, ONO-802 resembles $PGF_{2\alpha}$ in its contractile effect on the uterus in nonpregnant and pregnant rats and hamsters. It does not act through the nervous system, nor does it induce further PG release, but cAMP and calcium are involved in its action (322). Like PGE_1, ONO-802 causes abortion in rats in early and late pregnancy. Unlike the effects of PGE_2 and $PGF_{2\alpha}$ in animals, this abortifacient effect is not due to luteolysis. No consistent decrease in progesterone levels is associated with the uterine contractions that precipitate abortion (323).

Clinical trials of ONO-802 demonstrate its effectiveness and low incidence of side effects. Over 90 percent of 45 women 4 to 49 days past their expected menses aborted completely after receiving 20 to 40 μg of ONO-802 instilled into the uterus in either one or two doses. All but 10 were premedicated with atropine and pentazocine as analgesics; only 20 percent had nausea, 16 percent vomited, and 11 percent reported pain (428). Two trials involving women in early pregnancy employed .5 to 1.0 mg vaginal suppositories given every three hours for up to five doses, with similar results — 86 and 92 percent complete abortions. Side effects in these unpremedicated women included nausea in 2.2 percent, vomiting in 4 percent, diarrhea in 6 percent, and weakness in 4 percent (227). A trial with the same regimen in women 5 to 15 weeks pregnant achieved 89 percent effective abortions and 83 percent complete abortions. Ten percent of these women experienced nausea or vomiting; 25 percent, pain; 33 percent, diarrhea; and 10 percent, headache (445).

Clinical evaluation of ONO-802 is continuing in Japan and elsewhere. The ONO Pharmaceutical Company hopes to apply in 1980 to the Japanese drug regulatory agency for permission to market the PGE_1 analogue (449).

9-deoxo-16,16-dimethyl-9-methylene-PGE_2

A new PGE_2 derivative with both increased stability and enhanced uterine-stimulating activity is Upjohn's 9-deoxo-16,16-dimethyl-9-methylene-PGE_2 (see Figure 7). According to evidence from abortion studies in rhesus monkeys, tests for side effects in several animals, and preliminary clinical trials for second trimester abortion, the action of this agent is very specific to the uterus. In pregnant rhesus monkeys the threshold dose for uterine stimulation is 1 μg, or about one-fifteenth that of PGE_2 administered intravenously and one-twenty-fifth that of PGE_2 administered vaginally. Doses of 500 μg or more given in vaginal suppositories induced abortion. The monkeys showed neither gastrointestinal side effects nor appetite depression. Dose-response studies on colon activity in gerbils and gastric secretion, intestinal fluid pooling, and uterine activity in rats indicate that this agent is more specific to the uterus than PGE_2 (240).

In a preliminary clinical trial, 24 women in the second trimester of pregnancy received two vaginal suppositories, each containing 75 mg of the PGE_2 derivative, eight hours apart. Twenty

aborted within 24 hours, and one more within 26 hours. The women were not premedicated against side effects; 11 vomited and one had diarrhea (66). Doses of 60 mg are now being tested. This analogue has also reportedly proved effective in a small series for abortion in the early first trimester and for cervical dilatation in the first trimester (462).

Stable Analogues

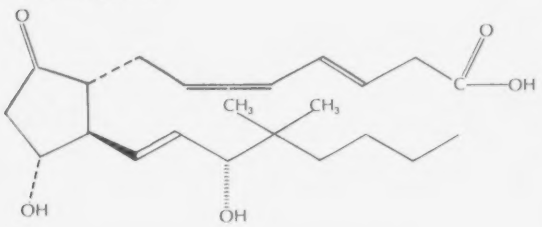
Imperial Chemical Industries (ICI) Ltd., Great Britain, has altered the 9-keto group on the PGE_2 ring to enhance the stability of several new derivatives. Replacing the unstable 9-keto group in the PGE ring with a 9-deoxy or 9β-phenoxy function improves stability. The new compounds show most of the activities of PGE_2 when assessed in a guinea pig abortion test on day 65 of pregnancy, a rat stomach acid test, and a PGE_2 receptor binding test in bovine corpus luteum in vitro (319).

Luteolytic PGs

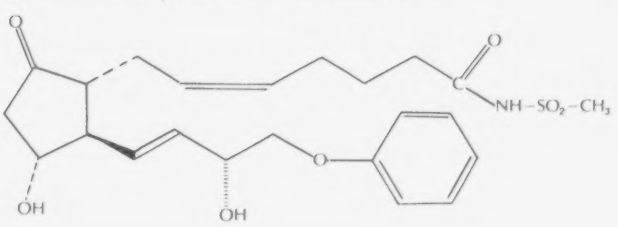
Two luteolytic, rather than uterus-stimulating, series of $PGF_{2\alpha}$ derivatives have been developed recently, one in the US, one in the Federal Republic of Germany. Results of animal studies are promising, but neither has yet been tested in women.

The luteolytic $PGF_{2\alpha}$ derivatives developed by John A. McCracken and colleagues at the Worcester Foundation for Experimental Biology in the US all have an acetylenic 13-dehydro structure (324). The most active compound is 16-fluoro-13-dehydro-$PGF_{2\alpha}$ (see Figure 7). This analogue was assayed for luteolytic effects in sheep by autotransplanting an ovary to the neck, where progesterone release directly from the ovary can be monitored easily throughout the estrous cycle. In this assay, the new compound was 100 times as active intravenously as the parent $PGF_{2\alpha}$. In cycling monkeys (*Macaca*

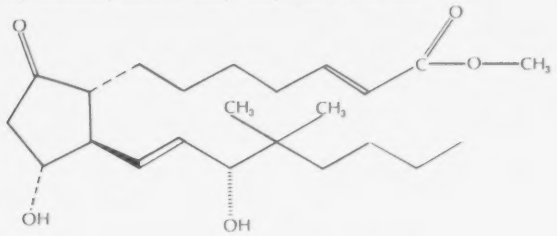
16,16-dimethyl-PGE_2



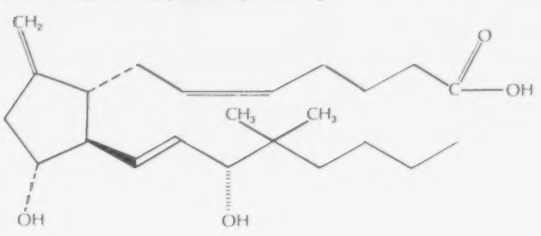
16-phenoxy-ω-tetranor-PGE_2 methylsulfonylamide (sulprostone)



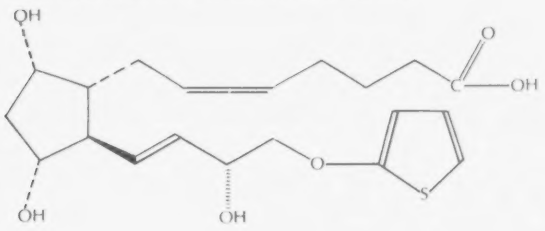
16, 16-dimethyl-trans-Δ^2-PGE_1 methyl ester (ONO-802)



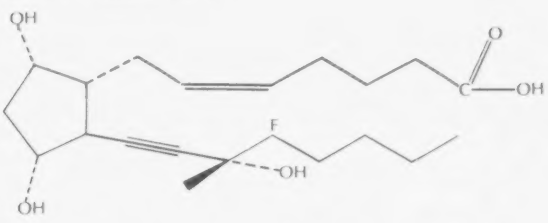
9-deoxo-16,16-dimethyl-9-methylene-PGE_2



17, 18, 19, 20-tetranor-16,-thienyloxy-$PGF_{2\alpha}$ (HR 837)



16-fluoro-13-dehydro-$PGF_{2\alpha}$



9β-phenoxy-16,16-dimethyl-16-m-chloro-phenoxy-ω-tetranor-PGE_2
(ICI 132, 932)

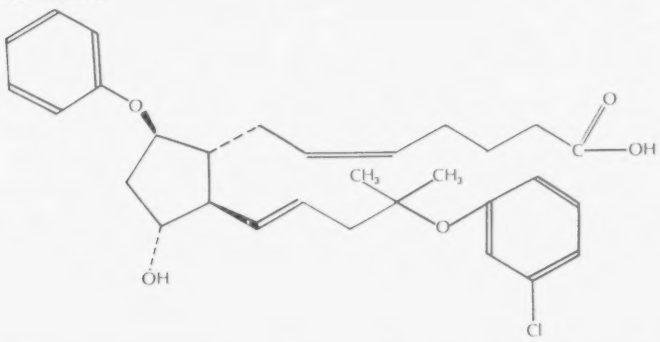


Figure 7. Various newly developed PG analogues promise to be longer acting, more potent, and more specific, with fewer side effects, than the prostaglandins now available. Some may yet prove to have a luteolytic effect in women.

fascicularis), 5 μg of 13-dehydro-$PGF_{2\alpha}$ infused for six hours caused luteolysis in the midluteal phase of the menstrual cycle, and the 16-fluoro derivative was even more potent. Luteolytic doses caused little or no uterine activity in sheep, and in monkeys as much as 2 mg intravenously failed to start uterine contractions. These observations suggest that in new PG analogues luteolytic action can be separated from uterus-stimulating action (324).

Scientists at Hoechst AG, Frankfurt-am-Main, Federal Republic of Germany, have synthesized another series of luteolytic $PGF_{2\alpha}$ derivatives. The most effective compound is HR 837 (17,18,19,20-tetranor-16$_a$-thienyloxy-$PGF_{2\alpha}$). When injected into hamsters in single subcutaneous doses on days four, five, and six of pregnancy, this analogue proved about 100 times as effective in terminating pregnancy as $PGF_{2\alpha}$. A dose of 0.2 mg/day aborted 50 percent of the animals. HR 837 was also luteolytic in pseudopregnant rats and heifers and in cycling and pregnant guinea pigs (379). The rat stomach strip screening test for gastrointestinal activity, which suggests the frequency of gastrointestinal side effects, found this agent only three to four times as potent as $PGF_{2\alpha}$. The ethoxyethyl ester of the 16-thienyloxy $PGF_{2\alpha}$ analogue was 400 times as effective a luteolysin as $PGF_{2\alpha}$. Several other variations, such as a β orientation of the thienyloxy group, replacing the ether linkage with other types of linking groups, or varying the chain length, produced compounds with less luteolytic activity, although some were still more active than the natural $PGF_{2\alpha}$ (12). Comparisons, like these, of the activities of various newly synthesized PGs can lead to an understanding of which chemical structures on the molecule are responsible for which biological effects.

The currently available natural PGs and analogues compete with other techniques in a variety of uses — particularly induction of labor, cervical dilation, second trimester abortion, and various complications of pregnancy. The promising derivatives developed in recent years and newer analogues not yet tested may some day supplant present techniques. Already PGs are a preferred method for treatment of mole, missed abortion, and fetal death. If research can produce more analogues with the desired combination of features — potency, specificity, prolonged action, and stability — and if these products can be made fully available so that health care providers and health care consumers will be able to choose the most appropriate procedures for any given need — then the role of prostaglandins in reproductive health care will surely grow.

The need to keep PGE_2 suppositories deep-frozen, as the package warns, limits their use to facilities with refrigeration.

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